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TIME-COURSES OF CHANGES IN
VENTILATION AND ARTERIAL GAS
TENSIONS IN MAN INDUCED
BY MODERATE EXERCISE

BY

GEORG MATELL



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STOCKHOLM 1963

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GEORG MATELL

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I. PREFACE

The present investigation is part of a research project dealing with the influences of various stress factors on the pulmonary gas exchange and on the control of respiration. The experimental part of the investigation was carried out in 1961.

It is a pleasure to record my gratitude to Professor U. S. v. EULER, Head of the Department of Physiology I, who originally introduced me to the physiology of respiration and evoked my interest in this field of research. I also wish to convey my sincere thanks to Drs. H. BJURSTEDT and C. M. HESSER, who have been my teachers since I joined their research groups in 1958 and who have generously placed the facilities of their laboratories at my disposal.

Finally, I would like to express my heartfelt thanks to members of the laboratory staff whose never-failing interest and collaboration made the experiments possible, and to J. BRISMAR, M. K., who assisted in the processing of the experimental data.

Stockholm, April 1963.

GEORG MATELL

II. INTRODUCTION

Seventy-five years have passed since GEPPERT and ZUNTZ in 1888 published their classical studies on the mechanisms involved in the hyperpnea of exercise. The wealth of literature available to-day on this engrossing subject has undoubtedly increased our knowledge of the numerous factors and influences which have to be considered. In spite of the efforts devoted to elucidating the nature of exercise hyperpnea, and the greatly increased interest prompted during recent years by the development of new tools for its study, many basic questions pertinent to the basic problem still remain unsettled.

The present investigation is a study of certain dynamic characteristics of ventilatory and blood chemical changes in man resulting from moderate, constant-load, dynamic exercise. On the whole, information is lacking as to the interrelations between the time-courses of ventilation and arterial O_2 and CO_2 tensions during constant-load exercise and subsequent recovery. In the present work continuous and simultaneous recordings of *i. a.* pulmonary ventilation and arterial O_2 saturation and pH have been used to permit a study of the above-mentioned interrelationships and of the interdependence of ventilation and blood chemical changes. The study has been devoted especially to the changes at the transitions from rest to work and from work to rest, since such changes were expected to be more informative than those observed in the steady state of ventilation.

In order to judge, if possible, the relative importance of the H^+ - CO_2 complex, and of its components, in eliciting and maintaining exercise hyperpnea, the changes resulting from a given work load were also compared with those observed during CO_2 inhalation and after the bicarbonate content of blood had been artificially changed by ingestion of ammonium chloride and sodium bicarbonate, respectively.

List of Symbols and Abbreviations

Primary Symbols

- V Gas volume in general
 $\dot{V}$ Gas volume per unit time
P Pressure in general, including partial pressure
S Oxygen saturation of hemoglobin, per cent
F Fractional concentration in dry gas phase

Suffixes

(a) Gas phase

- I Inspired gas
A Alveolar gas
E Expired gas
T Tidal gas

(b) Blood phase

- a Arterial
v Venous

The above symbols are those of the Atlantic City Convention (PAPPENHEIMER *et al.* 1950).

Some Other Symbols

- STPD Standard temperature and pressure, dry (0° C, 760 mm Hg)
BTPS Body temperature and pressure, saturated with water vapor
BHCO_{3St} The plasma bicarbonate content (mM/l) of blood under standard conditions,
i. e. at 37°, pH 7.4, and saturated with oxygen.
NB Normal BHCO_{3St}
HB High BHCO_{3St}
LB Low BHCO_{3St}
BSA Body surface area, m²

Other symbols are defined in the text as they occur.

Gas volumes are expressed in liters at the true volumes in the body (BTPS), except $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ which are expressed in l/min STPD. $\dot{V}_I$ is expressed in liters BTPS/min/m² BSA except when otherwise stated. Gas tensions are given in mm Hg at actual body temperature.

1 kpm = normal gravitational force on 1 kg

1 kpm/min = 0.163 W = 7.32 ft. lb/min

III. BACKGROUND

As an introduction to the problems dealt with in the present work, a short survey of certain earlier investigations will first be given on changes in arterial blood gas levels during exercise. Subsequently, other investigations will be reviewed which pertain to the interaction of humoral and non-humoral stimuli involved in exercise hyperpnea. The text is not intended to supply a detailed account of the numerous investigations dealing with these topics. For the sake of clarity only such contributions are included which were considered essential for the framing of the problems.

The current interest in topics dealing with the mechanisms underlying the hyperpnea of exercise is reflected in several excellent reviews which have appeared during the last few years. For a more detailed analysis of the various aspects of the hyperpnea of exercise, the reader may consult the recent reviews presented by DEJOURS (1959 and 1962), and by LAMBERTSEN (1961) and by several authors in "The Regulation of Human Respiration" (Proceedings of the J. S. Haldane Centenary Meeting in Oxford 1961) and in the British Medical Bulletin (January 1963).

Effects of Exercise on Arterial Blood Gases and Acid-Base Balance

Numerous attempts have been made to evaluate the roles of the known blood-borne respiratory stimuli in the initiation and maintenance of exercise hyperpnea. The majority of these investigations have been focussed on changes in the arterial blood, as judged either by analysis of alveolar gas or by direct determination of blood gases and acid-base balance following "spot-sampling" of arterial blood.

A perusal of the results obtained by use of the above-mentioned methods makes it evident that there is a lack of agreement as to the magnitude and direction of deviations in alveolar or arterial gas tensions resulting from exercise. Thus, in submaximal work, several investigators have found an increase in the alveolar P_{CO_2} (HALDANE and PRIESTLEY 1905, DOUGLAS and HALDANE 1912, ASMUSSEN and NIELSEN 1946, SUSKIND *et al.* 1950, BANNISTER *et al.* 1954), whereas others have observed a fall (*cf.* COMROE 1944). A rise in the arterial P_{CO_2} was observed by SUSKIND *et al.* (1950) and HICKAM *et al.* (1951). BARTELS *et al.* (1955) reported a fall in the arterial P_{CO_2} , whereas other authors have found only slight fluctuations within the normal range of variation (LILIENTHAL *et al.* 1946, FILLEY *et al.* 1954, ASMUSSEN and NIELSEN 1958, HOLMGREN and LINDERHOLM 1958).

Direct determinations of the arterial pH during exercise have yielded more consistent results. Already in 1923 ARBORELIUS and LILJESTRAND as well as

BARR, HIMWICH and GREEN demonstrated an increased acidity of the arterial blood during exercise. In recent years, with the advent of refined measuring techniques for blood pH, several investigators have confirmed the occurrence of acidemia during exercise; spot-sampling techniques were used almost exclusively. The bulk of evidence is in favour of a slight shift towards acidosis during moderate exercise (GALDSTON and WOLLACK 1947, HICKAM *et al.* 1951, FILLEY, GREGOIRE and WRIGHT 1954, BARTELS *et al.* 1955, ASMUSSEN and NIELSEN 1958, BARR *et al.* 1963), the shift being more marked during heavy and exhausting work (MITCHELL, SPROULE and CHAPMAN 1958, HOLMGREN and LINDERHOLM 1958, LAMBERTSEN *et al.* 1959).

Opinions also differ with respect to the effects on the alveolar P_{O_2} . An increase during submaximal work has been reported by LILIENTHAL *et al.* (1946), FILLEY *et al.* (1954), BARTELS *et al.* (1955), whereas SUSKIND *et al.* (1950) observed a fall in the alveolar P_{O_2} . Direct determinations of the arterial P_{O_2} have generally shown rather small changes during exercise, although there is less agreement as to the direction of the changes. Thus, a rise was observed by BARTELS *et al.* (1955) and LAMBERTSEN *et al.* (1959), while LILIENTHAL *et al.* (1946), SUSKIND *et al.* (1950), FILLEY *et al.* (1954), HOLMGREN and LINDERHOLM (1958) have reported a fall in the arterial P_{O_2} . ASMUSSEN and NIELSEN (1958) and MITCHELL *et al.* (1958) found no significant change in the arterial P_{O_2} during exercise. For exhausting exercise, HOLMGREN and LINDERHOLM (1958) reported an impressive fall in the arterial P_{O_2} (22 mm Hg).

There are as yet relatively few investigations in which alveolar or arterial P_{CO_2} and P_{O_2} , or arterial pH, have been followed by means of consecutive or continuous measurements during the course of exercise. RAHN and OTIS (1949), who plotted the alveolar tensions as a function of time on the CO_2 - O_2 diagram, observed an initial lowering of the alveolar P_{O_2} and an increase in the alveolar P_{CO_2} . SUSKIND *et al.* (1950) described a similar initial course for the arterial gas tensions. BARR *et al.* (1963) studied the time-courses of blood gas changes during moderate, constant-load exercise in man, using techniques for continuous and simultaneous recordings of arterial O_2 saturation and pH. Quantitative ventilatory measurements were avoided in order not to interfere with the normal respiratory pattern. After an initial drop during the first 1.5 min of exercise the calculated arterial P_{O_2} increased by about 5 mm Hg to reach a plateau in the 3rd–6th min of exercise. The arterial pH was lowered by about 0.04 units. It was noted that the arterial gas tensions and pH remained unchanged during the first half-minute of exercise and recovery.

Interaction of Humoral and Non-Humoral Stimuli in the Hyperpnea of Exercise

Ventilatory responses to the H^+ - CO_2 complex. It is a well-known fact that in resting man the ventilatory response to changes in the arterial $[H^+]$ and P_{CO_2} , as produced by inhalation of CO_2 , is characteristically linear over a certain range of arterial $[H^+]$ or P_{CO_2} values (*cf.* LAMBERTSEN *et al.* 1953, SCHAEFER

1958). The slope of the CO_2 -response curve, as well as its transposition to the left or right in acid-base displacements have been studied extensively by several investigators (NIELSEN 1936b, NIELSEN and SMITH 1951, ALEXANDER *et al.* 1955, LERCHE *et al.* 1959, CUNNINGHAM *et al.* 1961). That the resting CO_2 -response curve becomes steeper under the influence of hypoxia has been shown by NIELSEN and SMITH (1951) and by many others (*cf.* LLOYD 1963), although KELLOG *et al.* (1957) found the slope to be unchanged in acclimatized subjects.

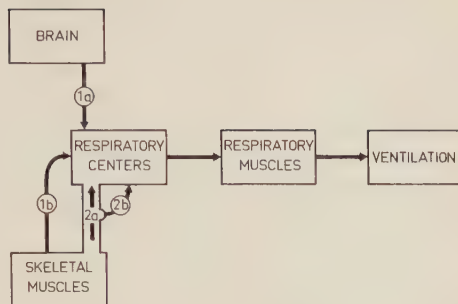
The ventilatory response to CO_2 inhalation has also been investigated during exercise and found to be the same as at rest. During exercise, however, the rectilinear part of the stimulus-response curve is displaced to the left of the resting curve (NIELSEN 1936b, CRAIG 1955, NIELSEN and ASMUSSEN 1963), the more so the higher the work intensity (ASMUSSEN and NIELSEN 1957). NIELSEN and ASMUSSEN (1963) have demonstrated evidence for the existence of a CO_2 threshold during exercise, which must be surpassed before ventilation is stimulated by CO_2 .

Information is scanty as to the effects of metabolic acid-base displacements on the ventilatory response to exercise. HALDANE in 1921 noted severe panting during exercise under ammonium chloride acidosis. DENNIG *et al.* (1930) observed, in one subject, an increased ventilatory response to exercise after ingestion of ammonium chloride, and conversely, a slightly diminished ventilatory response during alkalosis. REFSUM (1961) observed, also in one subject, an enormous ventilation in one-minute exercise tests after ingestion of ammonium chloride. In the mentioned investigations the magnitude of the acid-base displacements was considerable, however.

It is of special interest to consider what the ventilation of a resting man would be if his blood had the same acid-base composition as would occur during exercise. It would then be possible to quantitatively express the non-humoral drive in exercise hyperpnea by subtracting the chemically accountable ventilation from that actually measured during exercise. This approach has been used by CUNNINGHAM (1963). Such calculations showed that the average changes reported to occur in the H^+ - CO_2 complex in exercise of various severities (assuming the arterial oxygen tension to be the same for rest and exercise) could be expected to yield, in the resting subject, a ventilation that would amount to about 60 % of the exercise ventilation. It was pointed out that this estimate was based on certain assumptions as to the slope of the CO_2 -response curve and that the effect of raised body temperature was not included in the calculations.

Some features of the combined neuro-humoral concept. The older notions that a single, dominant mechanism was responsible for the hyperpnea of exercise, *e. g.* chemical (HALDANE and PRIESTLEY 1905, WINTERSTEIN 1911, DOUGLAS 1914) or neurogenic (reflex or cortical), have gradually been abandoned in favour of the more recent concept of a multiplicity of regulating factors (for

Fig. 1. Schematic representation of factors and pathways involved in the mechanism of exercise hyperpnea (modified from DEJOURS 1959). Overriding control functions (1a) interact with reflex influence originating in the muscles (1b) and with blood-borne stimuli (chemical, as *e. g.* $[H^+]$, CO_2 , O_2 , catecholamines, and physical, as *e. g.* body temperature and blood pressure), which either act directly on the respiratory centers (2a) or via peripheral chemo- or baroreflexes (2b).



reviews, see COMROE 1944, GRAY 1950, GRODINS 1950, WINTERSTEIN 1955, SCHMIDT 1956, DEJOURS 1959, LAMBERTSEN 1961, CUNNINGHAM 1963).

Fig. 1 shows postulated nervous pathways, along which (1a) overriding control is exerted from higher levels in the brain, and (1b) reflex influence from musculoskeletal receptors are mediated. Also represented are the pathways through which blood chemical changes, caused by the production of metabolites in the working muscles, may influence the activity of the centers. These chemical changes ("blood-borne" stimuli) may exert their action directly via the blood perfusing the centers (2a) or by reflex influence (2b) originating in peripheral chemo- or baroreceptors.

That the hyperpnea of exercise cannot be fully explained in terms of the well-known stimuli to breathing (CO_2 , blood and tissue acidity and hypoxia) or other known chemical changes related to metabolism has thus long been recognized by different groups of investigators. Certain interrelations between other factors capable of modifying ventilation and some characteristics of exercise hyperpnea are illustrative in this respect.

Thus, by using the relatively simple approach of studying the time-course of the ventilatory response to exercise, it has been possible to draw certain conclusions as to the import of factors other than chemical. This approach was probably first used by KROGH and LINDHARD (1913b), who observed that ventilation rises very quickly at the onset of exercise. They concluded that the initial ventilatory change occurred too rapidly to result from any action of blood-borne stimuli on the respiratory center.

The observations of KROGH and LINDHARD have in the main been confirmed by more recent investigations. Thus, a sudden onset of light, dynamic exercise has been shown to result in an immediate increase in ventilation (ASMUSSEN and NIELSEN 1948, DEJOURS *et al.* 1955a). In its further time-course, ventilation first remains relatively constant during the 20–30 seconds following the onset of exercise and then shows a secondary increase to a plateau (DEJOURS 1963). With a sudden transition from exercise to rest, ventilation again falls abruptly (ASMUSSEN and NIELSEN 1948, DEJOURS *et al.* 1955a), and then

remains essentially constant at a higher than pre-exercise level for 20—30 seconds before returning gradually to normal. The sequence of ventilatory changes is characteristic for periods of light to moderate dynamic exercise under constant load.

It is the consensus of opinion that both the initial rise and terminal fall of exercise hyperpnea must be neurogenic in nature ("fast component" of DEJOURS), and that the neurogenic control of ventilation in these phases is at least partially exerted via proprioceptive reflexes from muscles and tendons in the moving limbs (HARRISON, CALHOUN and HARRISON 1932, KAO, SCHLIG and BROOKS 1955, HUTT, HORWATH and SPURR 1958, DEJOURS 1959, DEJOURS, BECHTEL-LABROUSSE and RAYNAUD 1961). The rapid ventilatory changes at the start and cessation of exercise have been further investigated on a quantitative basis (for reviews, see DEJOURS 1959 and 1963). In general, the fast component has been found to increase somewhat with increasing work loads and to be greater at the cessation of exercise than at its start.

The slower phases of the changes in ventilation during exercise and recovery have been connected with both cortical control and with reflex and blood-borne influences from the working muscles (for reviews, see DEJOURS 1963, KAO 1963, NIELSEN and ASMUSSEN 1963).

Studies of the slow phase of recovery may be rewarding in attempts to distinguish between humoral and non-humoral stimuli. By "autotransfusion of work blood" ASMUSSEN and NIELSEN (1950) obtained evidence that the blood during heavy exercise contained specific substances with a stimulatory effect on ventilation.

In similar experiments, DEJOURS, MITHOEFER and TEILLAC (1955b) trapped blood in the legs by inflation of cuffs at the end of light exercise and observed, on release of the cuff pressure during recovery, that hyperpnea occurred sharply after a long delay of 18 seconds, *i. e.* not before the blood liberated from the occluded limbs had reached the arterial side. Conversely, if cuffs around the thighs were inflated just before exercise ($\dot{V}_{O_2}$ about 0.4 l/min) was stopped, ventilation and alveolar P_{CO_2} fell below resting levels, indicating withdrawal of the normal stimulation to respiration in recovery (DEJOURS, MITHOEFER and RAYNAUD 1957b). A final assessment of the relative importance of humoral and non-humoral stimuli during exercise and recovery will have to await experimental analysis of the time-course of ventilatory and blood chemical changes, as pointed out by TEILLAC and LEFRANÇOIS (1962). With certain assumptions previously mentioned (p. 10), CUNNINGHAM (1963) estimates that "hypothetical resting men whose bloods have the same compositions as those of the exercising subjects would, in most cases, have approximately the same ventilations as would be expected a few seconds after the end of exercise, immediately after the completion of the rapid phase of recovery but before change in the composition of the blood in the receptor areas could occur".

IV. PROBLEMS

From the investigations mentioned in the preceding review it is evident that the long-standing uncertainty as to the changes in arterial P_{CO_2} , pH and P_{O_2} occurring during exercise has been a major source of earlier disagreements as to the possible interdependence of ventilatory and blood chemical responses to exercise. This uncertainty has made it difficult to appraise quantitatively the various neurogenic and chemical factors which may be responsible for *e. g.* the components postulated by the neuro-humoral theory.

1. Recent investigations performed in this laboratory on human subjects, by use of continuous recording techniques, have shown relatively consistent changes in the arterial blood gases and pH during constant-load, moderate exercise and ensuing recovery; it became evident that (a) some of the earlier discrepancies may be explained by the observation that the normal oscillations in arterial gas tension levels at rest may be sufficiently great to necessitate caution in drawing conclusions based on results from "spot-sampling" of arterial blood, and (b) the arterial pH and O_2 saturation displayed characteristic time-courses during the periods of exercise and recovery.

It therefore seemed worthwhile to reinvestigate the interdependence of ventilatory and arterial chemical changes in the different phases of constant-load, moderate exercise, using continuous recording techniques for an analysis of the relations between these changes.

2. The quantitative appraisal of possible chemical and neurogenic stimuli in exercise hyperpnea has also suffered from the lack of consistent data as to the true changes in arterial blood gases and acid-base balance. In addition, the possible participation of blood-borne H^+ and CO_2 in the initiation and maintenance of exercise hyperpnea has been obscured by the scarcity of data relating metabolic, ventilatory and blood chemical alterations in a single group of subjects.

Therefore, an attempt was made to assess quantitatively the possible stimulating effect of the $\text{H}^+\text{-CO}_2$ complex, in experiments in which the responses of ventilation and arterial $[\text{H}^+]$ and P_{CO_2} to constant-load, moderate exercise were compared with those observed during inhalation of CO_2 at rest. The study was extended to include an assessment of the H^+ and CO_2 stimuli in both types of hyperpnea after independent changes in their arterial levels by ingestion of ammonium chloride and sodium bicarbonate.

Although the responses to exercise were studied in conditions of normal, high and low $\text{BHCO}_{3\text{SI}}$, it should be stressed that the work was standardized throughout the investigation to 625 kpm/min for 6 min on the bicycle ergometer. The results obtained from the exercise experiments and the discussion of their possible physiological significance can accordingly not be generalized to hold for other work loads or for other types of work.

V. METHODS

The basic feature of the experimental approach was the continuous and simultaneous recording of tidal air and respiratory minute volume as well as arterial O_2 saturation and pH during constant-load, dynamic exercise and recovery. The ventilatory changes and the simultaneous blood chemical changes were compared with those obtained during CO_2 inhalation. In order to study the effects of changing the buffering capacity of the blood and tissues, the experiments were performed both when buffering capacity was normal ("NB") and after subchronic elevation and lowering of the $BHCO_{3st}$ were artificially induced. These conditions will subsequently be termed "HB" (high $BHCO_{3st}$) and "LB" (low $BHCO_{3st}$). The acid-base displacements were induced by ingestion of ammonium chloride and sodium bicarbonate (see p. 18) for three days prior to the experiments.

It was decided to use a moderate work load for several reasons. First, with moderate respiratory minute volumes it is possible to keep the breathing resistance of the measuring devices sufficiently low, so that the respiration is not significantly influenced. Second, it seemed desirable to avoid the increasing work of breathing that would accompany an otherwise constant load of heavy exercise (*cf.* LILJESTRAND 1918, NIELSEN 1936a, McKERROW and OTIS 1956, MARGARIA *et al.* 1960, MARSHALL 1962). Third, it was considered appropriate to avoid accumulation of large amounts of fixed acids in order to maintain, as far as possible, the initial acid-base condition.

The technique of recording continuously the arterial pH and O_2 saturation involved a loss of blood of about 8 ml per min, *i. e.* 250 ml for the completion of one experiment. According to GULLBRING *et al.* (1960) this loss would correspond to a decrease in the physical working capacity at pulse rate 170 (PWC_{170}) of about 75 kpm/min. No adverse effects of blood loss of this order of magnitude were observed on heart rate and blood pressure in an earlier investigation, in which the same recording techniques were used during exercise at 400 and 700 kpm/min (BARR *et al.* 1963).

The ventilatory response to CO_2 inhalation is linear over a limited range of CO_2 fractions (for reviews, see SCHAEFER 1958, LAMBERTSEN 1961). In the present experiments the CO_2 ventilatory response curves were investigated within this range. Two different CO_2 fractions were used for this purpose, the higher fraction being chosen so as to yield approximately the same $\dot{V}_I$ in the 9th and 10th minutes as was obtained in exercise during the steady state of ventilation.

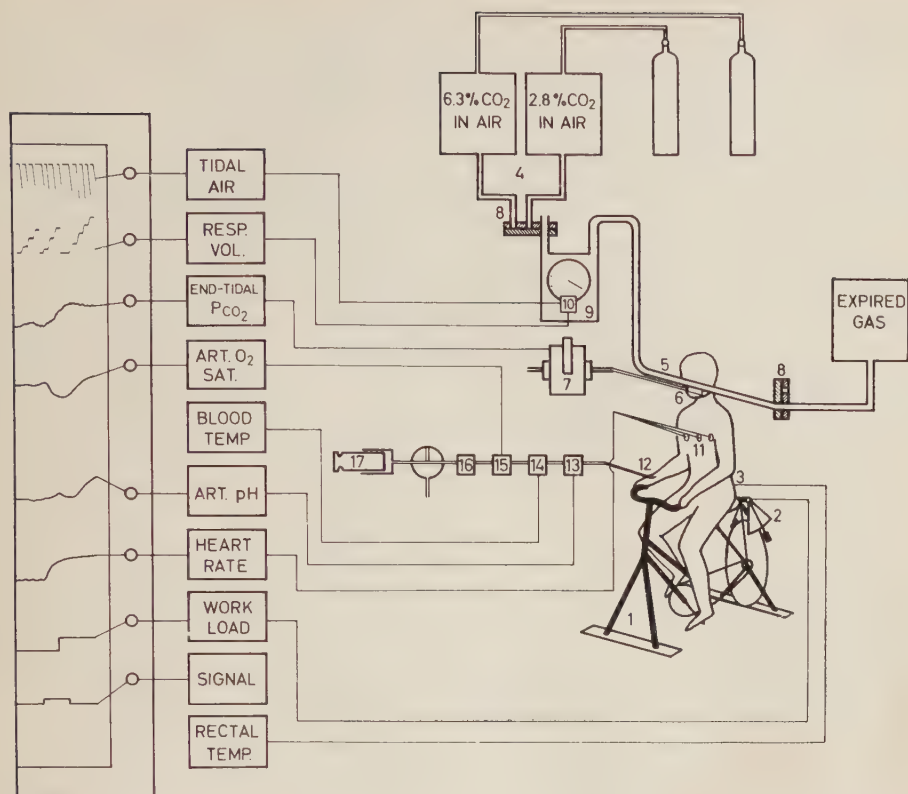


Fig. 2. Schematic diagram of experimental set-up. 1 = bicycle ergometer, 2 = braking load, 3 = thermistor for rectal temperature, 4 = plastic bags for gas mixtures, 5 = respiratory valves and mouth-piece, 6 = end-tidal gas sampler, 7 = CO_2 analyzer pick-up, 8 = three-way stopcock, 9 = gas meter, 10 = two-channel photoelectric pulse-adding device, 11 = electrodes for cardiometer, 12 = radial artery catheter, 13 = pH-sensing unit, 14 = thermistor, 15 = oximeter cuvette, 16 = roller pump and 17 = syringe for sampling of arterial blood.

Techniques

The general experimental arrangement is shown in Fig. 2. The variables listed below were inscribed continuously and simultaneously on photokymographic records at a paper speed of 1.25 mm/sec.

Inspired gas volumes were measured with a standard dry rotary gas meter (Nordgas), equipped with a fast electronic pulse-counting device (BJURSTEDT and LÖNN 1960) to permit continuous and accurate recording of *tidal volume* and *respiratory minute volume* (staircase curves).

End-tidal P_{CO_2} . End-tidal gas was sampled automatically, breath by breath, by means of a device described by BRISMAR, HESSER and MATELL (1962) and drawn through a rapid infrared CO_2 analyzer (Beckman-Spinco, model LB-1) at a constant flow of 100 cc/min. The end-tidal sampler was mounted on a low resistance and low dead space breathing valve, modified according to v. DÖBELN (1949). The *total external*

dead space amounted to 15 ml. The over-all external breathing resistance to a flow of 1 l/sec was 2.6 cm H₂O during inspiration and 0.9 cm H₂O during expiration. The CO₂ analyzer was calibrated with five known mixtures of CO₂ in air, saturated with water vapor.

pH and O₂ saturation of the arterial blood were recorded by a technique described in detail elsewhere (BARR and BJURSTEDT 1963). Arterial blood was drawn via a Teflon catheter inserted into the radial artery (BARR 1961) through the pH-oximeter assembly. The flow of blood was kept constant at a rate of 8 ml/min by means of a roller pump.

The dynamic response of the recording system was adjusted so that a square-wave change in arterial O₂ saturation and pH at the catheter tip in the radial artery resulted in 90 per cent galvanometer deflection after 6.8 sec, for both parameters.

By using a logarithmic amplifier (WIEDERHIELM 1956) a linear response to changes in arterial O₂ saturation was obtained. For each experiment three points on the calibration curve were obtained by equilibrating blood samples from the subject with known gas mixtures at 37° C and by passing these samples through the pH-oximeter sensing units. The galvanometer deflections were recorded and the levels of O₂ saturation calculated from the line charts of SEVERINGHAUS (1958). The drift of the oximeter assembly was virtually nil over the experimental periods. The technique permitted detection of changes in arterial O₂ saturation as small as 0.1 %.

Calibration of the pH electrode assembly was performed before and after each experiment using five 1/15 molar phosphate buffers (pH-range 7.00—7.60) (the same buffers were used for all the experiments) prepared according to HASTINGS and SENDROY (1924). The drift of the pH-electrode assembly was less than 0.001 pH during the experimental period.

The temperature of the blood passing the pH-electrode assembly was continuously recorded on an ink-writer to permit correction of the arterial pH to actual body temperature, using a correction factor of 0.0147 per degree C (ROSENTHAL 1948).

Heart rate was obtained by means of an instantaneous cardi tachometer (STURM and WOOD 1947).

Rectal temperature was followed by use of a thermistor unit.

Laboratory methods

Expired air was collected in plastic bags. Samples of expired air were withdrawn and stored under mercury for later analysis in duplicate according to SCHOLANDER (1947).

O₂ and CO₂ contents of arterial blood having just passed the pH-oximeter assembly were measured in duplicate according to VAN SLYKE and NEILL (1924). The maximal difference between duplicates was 0.2 vol. %. Corrections were made for syringe dead space.

Calculations

For calculation of changes in the arterial O₂ and CO₂ tensions, the recorded intra-individual changes in arterial pH and S_{O₂} were first reduced to time-averages over half-minute periods (first 3 minutes of exercise and first 2 minutes of recovery) and one-minute periods (3rd—6th minute of exercise and 2nd—6th minute of recovery). The corresponding arterial O₂ and CO₂ tensions were then calculated as follows.

Arterial O₂ tension (P_{aO₂}) (at body temperature) was computed from the values for arterial oxygen saturation, pH_a, and body temperature using the line charts of SEVERINGHAUS (1958).

Table I

Subject	Age (years)	Height (cm)	Weight (kg)	Body surface area ¹ (m ²)	Blood pressure (mm Hg)	
					Supine	Standing
R. H.....	22	184	65	1.86	140/90	140/90
J. B.....	22	178	75	1.93	130/80	130/80
A. F.....	21	174	68	1.82	130/80	130/80
E. T.....	22	182	67	1.87	125/80	125/80
B. F.....	25	175	61	1.74	105/70	100/70
B. S.....	26	190	76	2.02	105/70	105/70
J. F.....	23	181	64	1.82	130/90	125/85
M	23	181	68	1.87	124/80	122/79

¹ From nomogram of DUBOIS and DUBOIS (1916).

Arterial CO_2 tension (P_{aCO_2}) (at body temperature) was computed by means of the HENDERSON-HASSELBALCH equation from values of pH_{37° , plasma CO_2 -content and serum pK'_{37° for carbonic acid (obtained according to SEVERINGHAUS, STUFFEL and BRADLEY 1956). The solubility coefficient for CO_2 in plasma was assumed to be 0.521. The plasma CO_2 content was estimated from whole blood CO_2 content, the hemoglobin concentration, O_2 saturation and pH of arterial blood using the nomogram of VAN SLYKE and SENDROY (1928) and due correction factors (see PETERS and VAN SLYKE 1931, p. 939). P_{aCO_2} values thus obtained were transformed to body temperature according to BRADLEY, STUFFEL and SEVERINGHAUS (1956).

The same procedure was used to estimate $\text{BHCO}_3\text{:st}$ (the plasma bicarbonate content of blood under standard conditions, *i. e.* at 37° , pH 7.40 and saturated with oxygen).

In this way the $\text{BHCO}_3\text{:st}$ values at rest, during CO_2 breathing and during the 1st and 5th–6th min of exercise were obtained. The P_{aCO_2} values during the course of the exercise period were then calculated as described above, assuming a linear decrease between the two $\text{BHCO}_3\text{:st}$ values obtained during exercise. For the period of recovery, the calculation of P_{aCO_2} was based on the assumption that $\text{BHCO}_3\text{:st}$ again increased inversely with the postulated decay of blood lactic acid, *i. e.* with a half-time of 15 min (*cf.* DILL *et al.* 1935, HENRY and DeMOOR 1950, HUCKABEE 1958).

For the *statistical treatment of data* current conventions have been used for the calculation of arithmetical mean (M), standard deviation (S. D.) and standard error (S. E.).

The statistical significance of differences between means was evaluated by applying the t-test to the individual differences (*cf.* FISHER 1948). $P < .001$, $P < .01$, $P < .05$ denote highly significant, significant and probably significant differences, respectively.

Subjects and Experimental Procedure

Seven healthy male medical students served as test subjects. The physical characteristics of the subjects are presented in Table I.

Each subject participated in three experiments in which the procedure was the same. One month's interval was allowed for restoration of hemoglobin lost during the preceding experiment.

In two of these experiments the subject's acid-base balance had been altered by ingestion of ammonium chloride and sodium bicarbonate, respectively. Either compound was administered orally for three days, the daily dosage being 2.5 meq/kg body weight divided in four doses. The last dose was given in the morning, a few hours before the experiment was begun. The average daily dose of ammonium chloride was 9.1 g, the average total dose being 27.0 g. The average daily dose of sodium bicarbonate was 14.4 g, the average total dose being 42.4 g. The sequence of experiments was rotated among the subjects.

Four to five days before each experiment the subject's health and physical characteristics were assessed. The subject was then made thoroughly familiar with the course and various phases of the experiment.

All experiments were performed in the morning, the subject having previously had a light breakfast. The Teflon catheter was introduced percutaneously into the right radial artery under light infiltration anesthesia (BARR 1961). The catheter caused no pain or other inconvenience to the subject, who could move his wrist freely with the catheter in position. The subject rested in the supine position for half an hour, and was given 150 mg Heparin (Vitrum) intravenously to prevent clotting in the pH-oximeter sensing unit during the ensuing experiment.

The subject then sat up on the bicycle. The cardi tachometer electrodes were taped to his chest and the mouth-piece was placed in position. Finally, the radial artery catheter was connected with the pH-oximeter recording system. The first part of the experiment was devoted to assessing the responses to inhalation of CO_2 , while the subject rested on the bicycle. For this purpose two different gas mixtures saturated with water vapor were inhaled from plastic Douglas bags, continuously being supplied from large gas cylinders (*cf.* Fig. 2). The composition of the gas mixtures were the same throughout the investigation, and the Pco_2 of the inhaled air was checked at each experiment. The subject first inhaled a mixture of 2.8 % CO_2 in air for 10 min, and was then switched over to a mixture of 6.3 % CO_2 in air for another 10 min.

The subject then rested for 30 minutes in the supine position, breathing air. He then was again seated on the bicycle for the second part of the experiment, the exercise test. He first remained at rest for 10—15 min in the sitting position. He was not told when to start working more than a few seconds in advance. The subject, breathing air (relative humidity 50 %), then pedalled the bicycle for 6 minutes at 50 rpm with a work load of 625 kpm/min and then rested for 6 min while still seated on the bicycle.

Sampling of expired gas and of arterial blood for analysis (see "Laboratory methods", p. 16) was performed during the 9th—10th min on each gas mixture in the CO_2 test, during a 3 min period at rest, and during the last 2 min of exercise. Blood samples for analysis of CO_2 content were also drawn during the first minute of exercise.

On completion of the experiment, the subject rested supinely for about 20—30 min, during which period the radial artery catheter was pulled out and the wrist bandaged. His physical working capacity at pulse rate 170 (PWC_{170}) was then determined according to SjöSTRAND (1947) and WAHLUND (1948).

Barometric pressure averaged 756 mm Hg (range 748—763 mm Hg). The room temperature of the laboratory was kept within 1°C and averaged 24.4°C , the relative humidity being about 50 %.

VI. RESULTS

Introductory Observations

Before describing the time-courses obtained for ventilation and for various blood chemical parameters, it seems appropriate to communicate other relevant observations which were made during the course of the investigation. These concern (1) the validity of end-tidal P_{CO_2} as a measure of the arterial P_{CO_2} in exercise, (2) the effects of artificially-induced shifts in the acid-base balance on blood $BHCO_{3st}$ and on metabolic rate and heart rate and (3) the ventilatory and blood chemical responses to inhalation of CO_2 which will subsequently be compared with those obtaining in exercise and recovery.

End-tidal P_{CO_2} as a Measure of Arterial P_{CO_2} during Exercise

End-tidal gas is generally considered representative of mean alveolar air in the resting supine position. During motionless standing end-tidal P_{CO_2} becomes lower than the mean arterial P_{CO_2} (ULMER and REICHEL 1961, BJURSTEDT *et al.* 1962). Normal gravity thus produces shifts in the ventilation-perfusion ratios within the subdivisions of the lung, and an alveolar dead space develops secondary to impaired perfusion of apical regions (*cf.* RILEY *et al.* 1959).

It seems reasonable to expect that sitting on the bicycle at rest would also produce a measurable alveolar dead space effect. That such is the case was borne out by the present experiments, in which an average arterial to end-tidal CO_2 difference of 2.2 mm Hg was obtained. This difference is somewhat lower than that observed by BJURSTEDT *et al.* in motionless standing (2.8 mm Hg).

If CO_2 is added to the inspired air, the diluting effect of the alveolar dead space ventilation on the expired alveolar air will be diminished. In the present investigation this was demonstrated by the fact that the arterial to end-tidal P_{CO_2} difference decreased to practically zero, when the subjects, sitting quietly on the bicycle, inhaled a mixture of 2.8 % CO_2 in air. When 6.3 % CO_2 in air was administered, the end-tidal P_{CO_2} increased by an average of 15.4 mm Hg, whereas the average increase in mean arterial P_{CO_2} amounted to 12.3 mm Hg. As a result of the larger increase in end-tidal P_{CO_2} , the arterial to end-tidal P_{CO_2} difference became negative (— 0.9 mm Hg on an average). It is thus evident that the changes in arterial P_{CO_2} induced by CO_2 breathing would be overestimated if assessed from the changes in end-tidal P_{CO_2} in the sitting or erect position.

During exercise the arterial to end-tidal P_{CO_2} difference was also reversed. This "negative" difference was larger than during inhalation of 6.3 % CO_2 , averaging — 3.1 mm Hg at the end of exercise. The increase in end-tidal P_{CO_2} during the course of exercise averaged 8.4 mm Hg, but the concomitant change

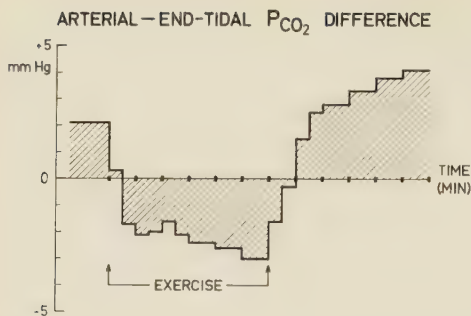


Fig. 3. The arterial to end-tidal P_{CO_2} difference during rest, exercise (625 kpm/min for 6 min) and recovery. Data obtained from continuous recordings (from 16 experiments in 7 subjects) have been reduced into group means of individual time-averages determined over the first six 30-sec periods in exercise and over the first four 30-sec periods in recovery. Other time-averages refer to 60-sec periods.

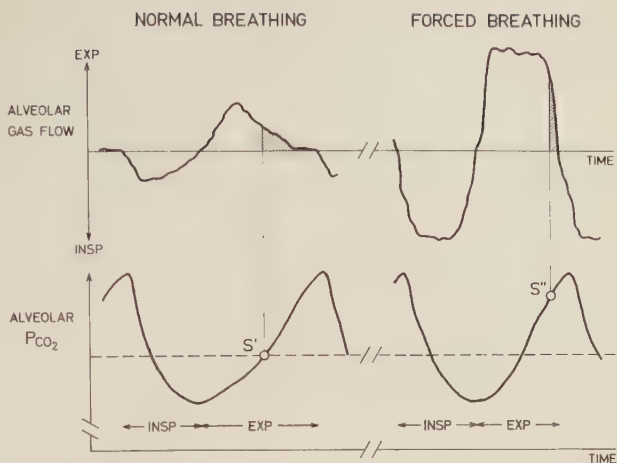
in arterial blood P_{CO_2} was only 3.1 mm Hg. The time-course of the observed mean changes in arterial to end-tidal P_{CO_2} difference during exercise and recovery is depicted graphically in Fig. 3. The reversal of the gradient occurred at the beginning of exercise; during recovery the gradient returned to the pre-exercise resting value within 2 min.

It is evident then that even breath-by-breath recordings of end-tidal P_{CO_2} do not give a true picture of the dynamic changes in P_{aCO_2} resulting from exercise. This observation is in agreement with the statement of KROGH and LINDHARD (1913a) that "the direct method of determining the composition of the alveolar air from samples taken at the end of inspiration and expiration becomes untrustworthy during muscular work".

Direct determinations during exercise of both end-tidal (end-expiratory) and arterial P_{CO_2} in the same individuals have been made by only a few investigators. SUSKIND *et al.* (1950) concluded that, on the whole, end-tidal and arterial P_{CO_2} changed in a more or less parallel fashion during exercise. In their Table 2, however, it can be seen that the arterial to end-tidal P_{CO_2} difference was + 2.1 mm Hg at rest, and - 1.8 mm Hg during exercise ($\dot{V}_{O_2}=0.596$ l/m²). In a study on the respiratory dead space during exercise, ASMUSSEN and NIELSEN (1956) found that during exercise with large tidal volumes (work load 360—1,080 kpm/min) the P_{CO_2} of end-expiratory samples was higher than that of simultaneously drawn arterial blood samples.

The observation of a reversed P_{CO_2} difference during forced breathing, as during CO_2 inhalation and exercise, may be explained as follows. The end-tidal sampler used in this investigation (BRISMAR, HESSER and MATELL 1962) as well as that described by RAHN *et al.* (1946) automatically delivers a small sample from a portion of expired air just beyond the expiratory valve. The small amount of gas sampled leaves the alveolar compartment within a very short period of time during expiration, and its composition relative to the mean alveolar air will thus be dependent both on the moment of sampling and on the concomitant slope of the alveolar P_{CO_2} curve (*cf.* Fig. 4) (*cf.* RAHN 1955).

Fig. 4. Schematic representation of time-courses of alveolar gas flow and P_{CO_2} during a respiratory cycle for normal and forced breathing. Hatched areas represent the portion of alveolar gas that fills the dead space at the end of an expiration (including dead space of valve). In normal breathing, the P_{CO_2} of the end-tidal sample (S') approximates that of mean alveolar air. In forced breathing, the end-tidal sample (S'') is drawn close to the end of expiration, and will thus yield an end-tidal P_{CO_2} that is higher than the mean alveolar P_{CO_2} .



The moment of sampling will in turn be dependent on the dead space/tidal volume ratio, as well as on the flow pattern during expiration. This is schematically illustrated in Fig. 4. The upper part of the figure shows the rate of flow of the alveolar gas as it leaves the alveolar compartment. The lower part of the figure shows the time course of P_{ACO_2} during a respiratory cycle and its mean value.

During *quiet breathing*, the midpoint of the period of sampling (S') falls near the middle of the time interval between minimal and maximal values of P_{ACO_2} . During *forced breathing*, induced *e. g.* by CO_2 breathing or exercise, the pattern of gas flow from the alveolar compartment *versus* time will be changed (TITSO 1935, CAIN and OTIS 1949), so that the time required to fill the dead space with alveolar gas at the end of expiration will be much shorter than during quiet breathing. This is the same as saying that the CO_2 molecules arriving beyond the expiratory valve at the end of the expiration have travelled more rapidly through the dead space. Hence, the interval between the time during which these molecules left the alveolar compartment (S'') and the time for maximal P_{ACO_2} must be shortened. The final result will then be that the end-tidal P_{CO_2} becomes higher than the arterial or mean alveolar P_{CO_2} , approximating the maximal alveolar P_{CO_2} occurring during the respiratory cycle.

The slope of the alveolar P_{CO_2} curve during expiration is another factor that determines the magnitude of the difference between end-tidal P_{CO_2} and mean P_{ACO_2} . This difference will be intimately related to the magnitude of the cyclic variations of alveolar P_{CO_2} within the respiratory cycle. DUBOIS, BRITT and FENN (1952) have described the theoretically expected variations at rest, on which the left part of the diagram in Fig. 4 is based. During exercise, much larger variations do occur, as has been theoretically predicted by YAMA-

Table II. Oxygen uptake, heart rate, standard bicarbonate and respiratory quotient at rest and
Conditions: *NB* = normal, *HB* = high $\text{BHCO}_3 \text{ St}$, *LB* = low $\text{BHCO}_3 \text{ St}$

	Oxygen uptake (1 STPD/min)			Heart rate (beats/min)		
	Rest ¹	Exercise ²	Difference Exercise— Rest	Rest ¹	Exercise ²	Difference Exercise— Rest
<i>NB</i>						
M ± S.E.	.311 ± .011	1.587 ± .044	+ 1.275 ± .037	78 ± 4	131 ± 5	+53 ± 4
S. D.	.030	.115	.099	11	13	12
P			< .001			< .001
<i>HB — NB</i>						
M ± S.E.	— .014 ± .017	+ .015 ± .084	+ .030 ± .074	4-8 ± 5	4-4 ± 6	4+5 ± 6
P	> .05	> .05	> .05	> .05	> .05	> .05
<i>LB — NB</i>						
M ± S.E.	+ .009 ± .016	+ .032 ± .034	+ .023 ± .028	+7 ± 3	+5 ± 5	-2 ± 3
P	> .05	> .05	> .05	> .05	> .05	> .05

¹ Mean value over 3 min.

² Mean of 5th and 6th min after onset of exercise.

MOTO (1960). BÜHLMANN (1961) has measured the increasing variations in the expired P_{CO_2} during exhausting exercise, and points out the difficulties in assessing the composition of the mean alveolar air during heavy exercise. In the present investigation the arterial to end-tidal P_{CO_2} difference amounted to — 3.1 mm Hg in the steady state of ventilation during exercise. The tidal and respiratory minute volumes were about the same as in experiments with inhalation of 6.3 % CO_2 (*cf.* above). Hence, the displacement in time of the alveolar gas sampling (S'') would be approximately the same in the exercise and CO_2 experiments. It may be inferred then that the larger part of the negative arterial to end-tidal P_{CO_2} difference during exercise would be due to the increasing variations in P_{ACO_2} within the respiratory cycle.

Theoretical calculations, similar to those of YAMAMOTO (*cf.* above) have been performed in this investigation using the measured values for ventilation and gas exchange, and assuming the measured end-tidal P_{CO_2} to be an approximation of the maximal P_{CO_2} during the respiratory cycle in forced breathing. The calculated difference between mean alveolar P_{CO_2} and the end-tidal

during exercise ($n = 7$, except when otherwise indicated)

Standard bicarbonate ³ (mM/l)			Respiratory quotient		
Rest ¹	Exercise ²	Difference Exercise— Rest	Rest ¹	Exercise ²	Difference Exercise— Rest
26.04 ± .65 1.71	24.17 ± .87 2.29	— 1.87 ± .33 .88 < .01	.777 ± .006 .015	.892 ± .023 .060	+ .114 ± .021 .055 < .01
+ 3.36 ± .36 < .001	+ 2.65 ± .40 < .001	— .71 ± .28 < .05	+ .003 ± .022 > .05	+ .009 ± .017 > .05	+ .005 ± .019 > .05
— 9.51 ± 1.13 < .001	— 9.52 ± 1.33 < .001	— .02 ± .40 > .05	— .001 ± .015 > .05	— .019 ± .017 > .05	— .018 ± .028 > .05

³ Plasma bicarbonate content of blood under standard condition, *i. e.* at 37°C, pH 7.40 and saturated with oxygen.

⁴ $n = 6$.

P_{CO_2} was found to be in good agreement with the directly measured arterial to end-tidal P_{CO_2} difference; during inhalation of 6.3 % CO_2 the measured difference was — 0.9 mm Hg and the calculated difference — 1.0 mm Hg. During exercise the measured difference was — 3.1 mm Hg and the calculated difference — 4.6 mm Hg.

It may be said in conclusion, that the present observation of a “negative” arterial to end-tidal CO_2 difference during exercise and during inhalation of CO_2 necessitates caution when attempting to estimate the level of the arterial P_{CO_2} (or mean alveolar P_{CO_2}) from measurements of the P_{CO_2} of end-tidal samples. This is even more the case in the transition from normal, quiet breathing when a “positive” arterial to end-tidal CO_2 difference exists because of an appreciable alveolar dead space. This is one reason why, in the present studies of time-related changes in arterial P_{CO_2} during exercise and recovery, reliance was placed on P_{aCO_2} values calculated from the arterial pH recordings rather than on end-tidal P_{CO_2} recordings.

Effects of Artificially Induced Shifts in the Acid-Base Balance on Oxygen Uptake, Heart Rate and Blood Bicarbonate

The work load was kept the same throughout the investigation in order to make possible a comparison between the ventilatory and blood chemical responses to exercise in conditions where shifts in the acid-base balance had been artificially induced. An account will be given below of the effects on the oxygen uptake, heart rate, standard bicarbonate and respiratory quotient observed in conditions of normal, high and low $\text{BHCO}_{3\text{st}}$, here termed "NB", "HB" and "LB", respectively. The changes observed are summarized in Table II.

Oxygen uptake. The deviations observed in O_2 uptake at rest in LB and HB were small and statistically insignificant. During the 5th—6th min of exercise the O_2 uptake had risen to an average of about 1.6 l/min. No significant differences were found between the three conditions. This was the case also for the increases in O_2 uptake as expressed per m^2 body surface.

Heart rate. At rest, the differences between NB and HB and between NB and LB were not statistically significant. The difference between HB and LB, however, was significant (not shown in Table II). By contrast, the increases in heart rate during exercise above resting values were similar in the three conditions.

Blood Bicarbonate. The shift in $\text{BHCO}_{3\text{st}}$ (expressed in mM/l) observed at rest after ingestion of ammonium chloride was more than twice that obtained after ingestion of equivalent amounts of sodium bicarbonate. During exercise a certain amount of lactic acid was presumably produced (*cf.* HUCKABEE 1958, HOLMGREN and STRÖM 1959), which caused a reduction of the $\text{BHCO}_{3\text{st}}$ in all three conditions. These reductions were statistically significant. The decrease was slightly larger in HB than in LB and NB. The $\text{BHCO}_{3\text{st}}$ was also determined during the first minute of exercise. The average decrease during the first minute in all three conditions was 0.34 mM/l ($P < 0.001$).

From the data presented above it can be concluded that the period of exercise (625 kpm/min for 6 min) involved about the same load in conditions NB, HB and LB. It is probable, however, that if the $\text{BHCO}_{3\text{st}}$ shifts had been more pronounced, an impairment in working performance would have resulted (*cf.* the experiments of DENNIG *et al.* (1930) and REFSUM (1961)).

Effects of Acid-Base Displacements on the $\Delta \dot{V}_I / \Delta [H^+]_a$ and $\Delta \dot{V}_I / \Delta P_{a\text{CO}_2}$ Slopes Resulting from CO_2 Inhalation

The results of inhalation of CO_2 -air mixtures at rest in conditions NB, HB and LB are summarized in Fig. 5. The oxygen fractions in the inspired air were chosen so as to minimize recorded changes in O_2 saturation of the arterial blood during the hyperpnea that resulted from inhalation of CO_2 -enriched air. The O_2 fraction was 0.18 in the gas with the low CO_2 fraction (0.028) and 0.16 in the gas with the higher CO_2 fraction (0.063). As can be seen in Tables III

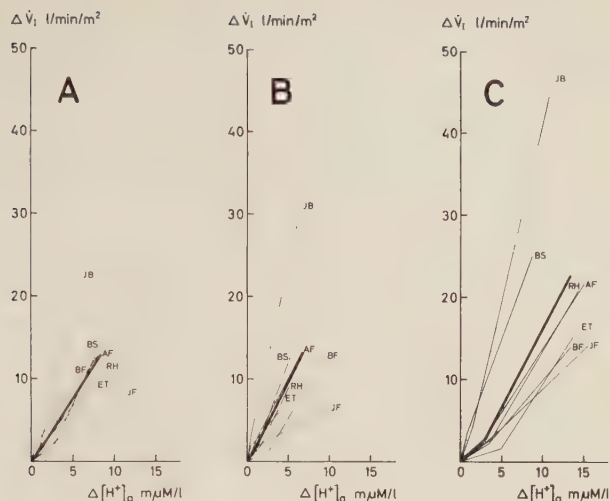
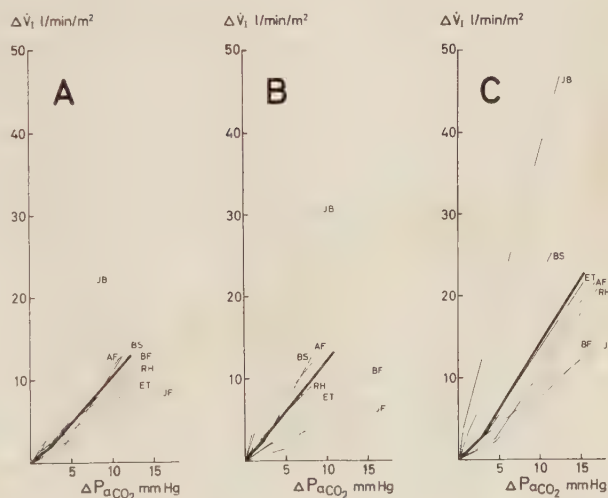


Fig. 5. Individual increments (from resting levels) in ventilation plotted against increments in arterial hydrogen ion concentration (upper 3 graphs) and in arterial carbon dioxide tension (lower 3 graphs).

Values were obtained during 9th and 10th min under inhalation of gas mixtures containing 2.8 and 6.3 per cent CO_2 in air.

Heavy lines indicate means of individual $\Delta \dot{V}_I / \Delta [H^+]_a$ and $\Delta \dot{V}_I / \Delta P_{aCO_2}$ slopes (*thin lines*).

A, B, and C denote normal, high and low $BHCO_3$ levels, respectively.



and IV, the O_2 saturation remained almost constant during CO_2 inhalation, whether studied in the NB, HB or LB conditions. The O_2 tension, however, showed greater changes, and an increased O_2 tension was evident during inhalation of 6.3 % CO_2 .

$\Delta \dot{V}_I / \Delta [H^+]_a$ Slopes (upper graphs in Fig. 5). The mean slopes were similar in the three conditions. A closer look at the upper three graphs in Fig. 5 reveals that the individual slope was nearly the same in all three conditions, although the absolute increments in ventilation and $[H^+]_a$ were greater in HB, and more so in LB, than in NB. On the average, an increase of $[H^+]_a$

Table III. Data obtained in 9th and 10th min of experiments on CO₂ breathing at rest (2.8 % Conditions: NB = normal, HB = high B_{HCO₃St}, LB = low B_{HCO₃St}

	$\dot{V}_I$ (1 BTPS/min/m ²)		V_T (1 BTPS/m ²)		S_{aO_2} (%)	
	2.8 % CO ₂	6.3 % CO ₂	2.8 % CO ₂	6.3 % CO ₂	2.8 % CO ₂	6.3 % CO ₂
<i>NB</i>						
M ± S.E.	6.34 ± .21	17.37 ± 1.71	.445 ± .022	.950 ± .074	96.1 ± .1	96.6 ± .1
S.D.	.54	4.53	.059	.196	.3	.4
<i>HB</i>						
M ± S.E.	6.15 ± .36	17.08 ± 3.19	.471 ± .014	1.021 ± .091	95.9 ± .2	96.6 ± .2
S.D.	.95	8.43	.036	.242	.5	.4
<i>LB</i>						
M ± S.E.	7.95 ± .43	27.84 ± 4.16	.576 ± .043	1.357 ± .081	96.2 ± .2	96.1 ± .2
S.D.	1.15	11.0	.114	.214	.5	.6
<i>HB - NB</i>						
M ± S.E.	— .18 ± .39	— .27 ± 1.50	+ .026 ± .016	+ .071 ± .023	— .2 ± .2	0 ± .2
P	> .05	> .05	> .05	< .05	> .05	> .05
<i>LB - NB</i>						
M ± S.E.	+ 1.61 ± .41	+ 10.49 ± 2.62	+ .131 ± .033	+ .408 ± .038	+ .1 ± .2	— .5 ± .3
P	< .01	< .01	< .01	< .001	> .05	> .05

¹ At body temperature.

² [H⁺]_a = hydrogen ion concentration of arterial blood in mμM/l.

35 mμM/l = pH 7.456, 40 mμM/l = pH 7.398, 45 mμM/l = pH 7.347, 50 mμM/l = pH 7.301.

by one mμM/l was associated with a ventilatory increase of 2.0 l/m² BSA in the three conditions.

$\Delta \dot{V}_I / \Delta P_{aCO_2}$ Slopes (lower graphs in Fig. 5). The mean slope was found to be steeper in LB than in the other two conditions. Otherwise, it can be seen from the lower graphs in Fig. 5, that the individual slopes show approximately the same sequence in the families of curves for the three conditions. The average ventilatory increase per mm Hg increase in P_{aCO_2} was 1.3 l/m² in NB, 1.4 l/m² in HB and 1.7 l/m² in LB.

and 6.3 % CO₂ in air); n = 7

[H ⁺] _a ^{1, 2} (mμM/l)		P _{aO₂} ^{1, 3} (mm Hg)		P _{aCO₂} ^{1, 4} (mm Hg)	
2.8 % CO ₂	6.3 % CO ₂	2.8 % CO ₂	6.3 % CO ₂	2.8 % CO ₂	6.3 % CO ₂
38.8 ± .6 1.7	45.7 ± .7 1.9	88.8 ± 1.5 4.0	101.7 ± 2.1 5.4	40.4 ± 1.0 2.7	50.2 ± .8 2.2
36.0 ± .6 1.7	41.5 ± .9 2.3	83.0 ± 1.3 3.3	96.5 ± 2.3 5.9	40.9 ± 1.1 3.0	49.7 ± 1.3 3.3
47.2 ± 1.6 4.2	57.6 ± 1.7 4.5	97.0 ± 2.7 7.1	104.3 ± 3.5 9.2	34.8 ± .6 1.5	47.3 ± .7 1.7
- 2.8 ± .5 < .01	- 4.1 ± .5 < .001	- 5.8 ± 1.6 < .01	- 5.2 ± 2.2 > .05	+ .5 ± 1.0 > .05	- .5 ± 1.0 > .05
+ 8.4 ± 1.8 < .01	+ 11.8 ± 1.9 < .001	+ 8.2 ± 4.1 > .05	+ 2.6 ± 5.3 > .05	- 5.6 ± .8 < .001	- 2.9 ± 1.0 < .05

³ Calculated from O₂-saturation and pH by use of the line charts of SEVERINGHAUS (1958).

⁴ Computed from the HENDERSON-HASSELBALCH equation.

Absolute mean values of the parameters studied in the 9th and 10th min of the CO₂ inhalation experiments are given in Table III.

In summary, the experiments with CO₂ breathing at two different levels of inhaled P_{CO₂} (2.8 and 6.3 % CO₂ in air) showed that the resulting ventilatory increment, as studied in normal, high and low BHCO_{3St}, was better correlated with the concomitant increment in [H⁺]_a than with that of P_{aCO₂}, for the individual as well as for the group.

Time-Courses of Ventilatory and Blood Chemical Responses to Constant-Load Exercise

In Fig. 7 the time-courses of different parameters during constant-load, dynamic exercise (625 kpm/min) and recovery are depicted graphically as obtained in the conditions of normal, high and low $\text{BHCO}_{3\text{st}}$. The graphs were based on data gathered from records as exemplified in Fig. 6. Absolute values (means) at rest and during exercise are given in Table IV.

Inspired Minute Volume. At the onset of exercise ventilation increased almost immediately. The initial rise was more rapid in HB and LB than in NB.

The initial rise was followed by a slower secondary increase, which continued until a plateau was attained within 3—4 min. The mean values in the 5th and 6th min (*cf.* Table IV) indicate that the ventilation became significantly greater in LB than in HB or NB, and that the difference between NB and HB was not significant.

At the cessation of exercise there was a sudden fall of ventilation followed by a smooth decay, the shape of which was similar in the three conditions. In the sixth minute of recovery the ventilation was increased by less than one liter/m² BSA above its pre-exercise level.

$[\text{H}^+]_a$. Fig. 7 shows the time-courses of individual and mean $[\text{H}^+]_a$ values, which were obtained from the arterial pH recordings. During the first half-minute of exercise $[\text{H}^+]_a$ remained essentially constant in NB as well as in HB and LB. Subsequently, the general trend was towards an acidotic shift in all three conditions. The absolute, mean values for $[\text{H}^+]_a$ at rest and during the 5th and 6th min of exercise in NB, HB and LB are given in Table IV.

At the cessation of exercise the mean $[\text{H}^+]_a$ remained essentially constant or increased somewhat during the first half-minute in all three conditions, and then decreased at a diminishing rate until the end of the recorded period of recovery when $[\text{H}^+]_a$ still remained well above the pre-exercise level.

$S_{a\text{O}_2}$ and $P_{a\text{O}_2}$. In the original recordings, the arterial O_2 saturation remained remarkably constant throughout the exercise and recovery periods (*cf.* Fig. 6). Small but consistent changes could, however, be detected. Thus, at the beginning of exercise, the $S_{a\text{O}_2}$ first increased somewhat and then fell below the resting level to a minimum, which was attained after some 60—90 sec. $S_{a\text{O}_2}$ then increased again, so that within the 5th and 6th min the pre-exercise level was reached (*cf.* Table IV). At the cessation of exercise $S_{a\text{O}_2}$ remained constant for about 30 sec. During recovery $S_{a\text{O}_2}$ rose to a maximum about 2 minutes after exercise and then declined again. This increase above the resting level amounted to an average of about 1 %.

The time-course of the oxygen tension showed the same general pattern as described above for $S_{a\text{O}_2}$, but the changes were considerably more marked (Fig. 7). At the onset of exercise $P_{a\text{O}_2}$ remained unchanged in the first half-

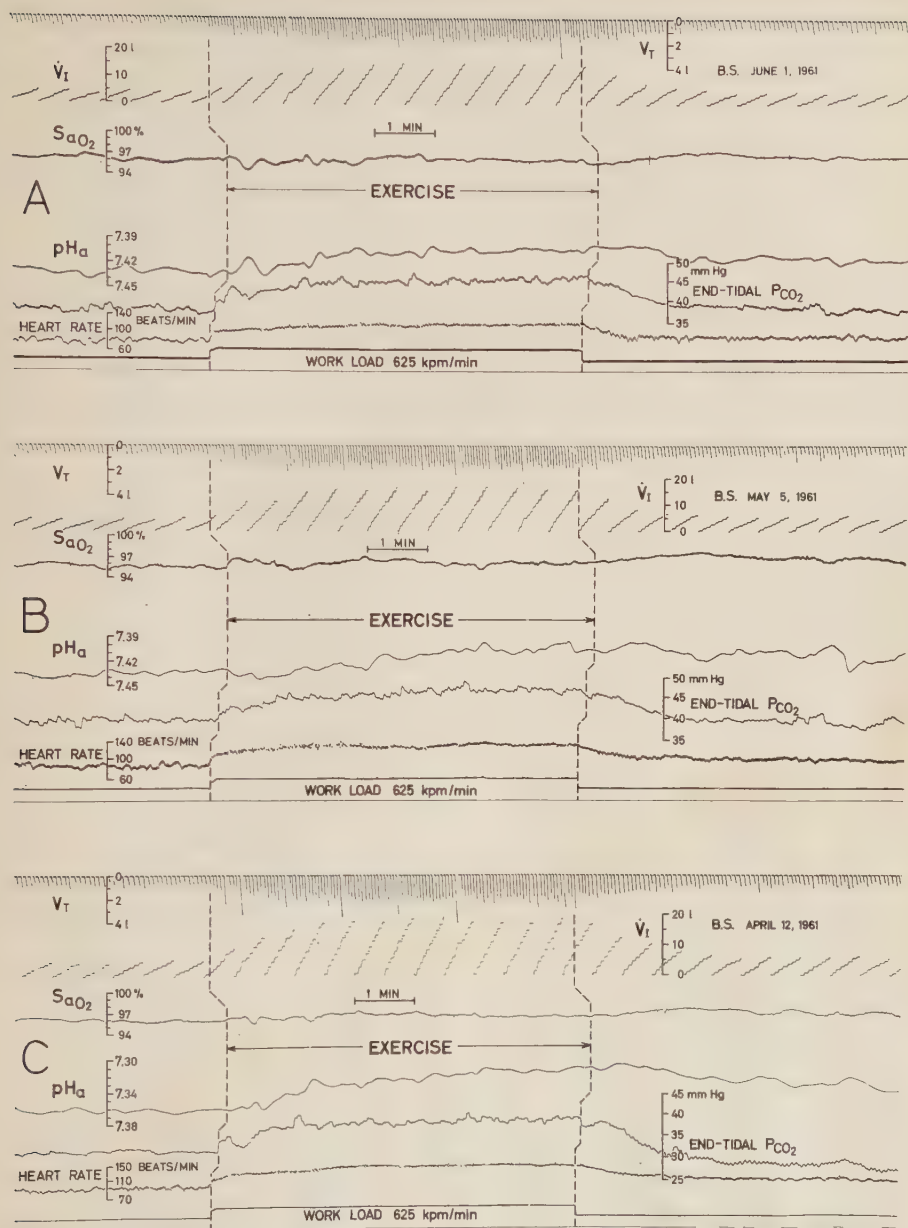


Fig. 6. Set of photokymographic recordings of responses in subject BS to constant-load exercise (625 kpm/min for 6 minutes) under conditions of normal BHC03St (A), high BHC03St (B), and low BHC03St (C) (length of records = 1/10 of original).

Dashed lines ("isotime" lines) indicate the delays in the SaO_2 , pH_a and end-tidal PCO_2 tracings.

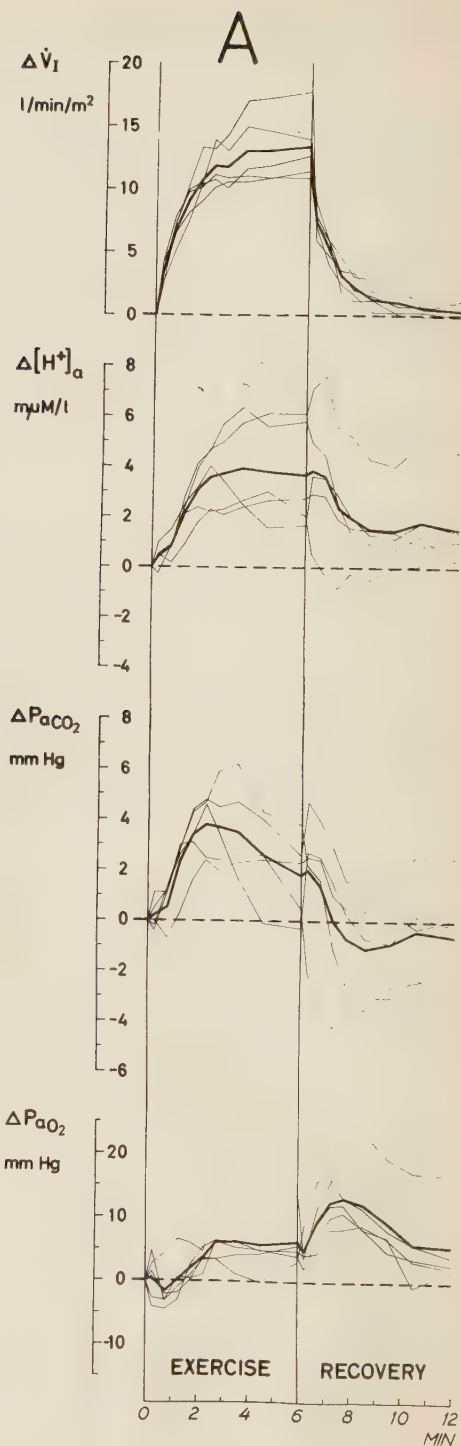


Fig. 7. Time-courses of deviations from resting values in (from above) $\dot{V}_I$, $[H^+]_a$, P_{aCO_2} and P_{aO_2} during exercise (625 kpm/min for 6 minutes) and recovery under normal $BHCO_{3St}$ (A, $n = 5$), high $BHCO_{3St}$ (B, $n = 5$) and low $BHCO_{3St}$ (C, $n = 6$).

Heavy lines show means of individual time-averages (thin lines) determined over successive 30-sec periods (first 3 min of exercise and first 2 min of recovery) and 60-sec periods (remaining phases of exercise and recovery).

In plotting the time-courses for blood chemical changes due allowance has been made for the delays in the recordings (cf. Fig. 6).

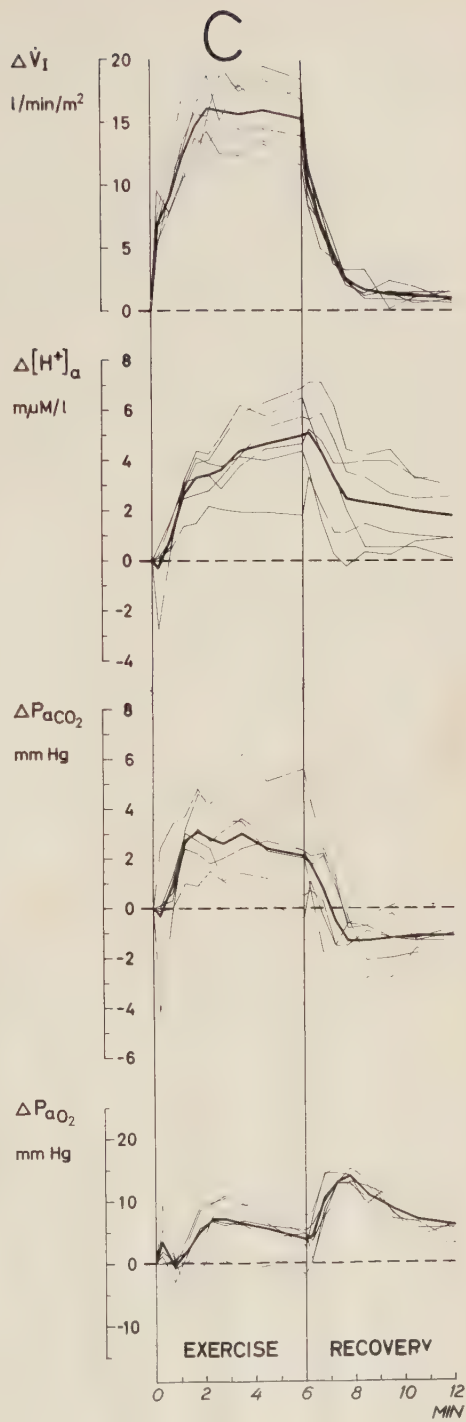
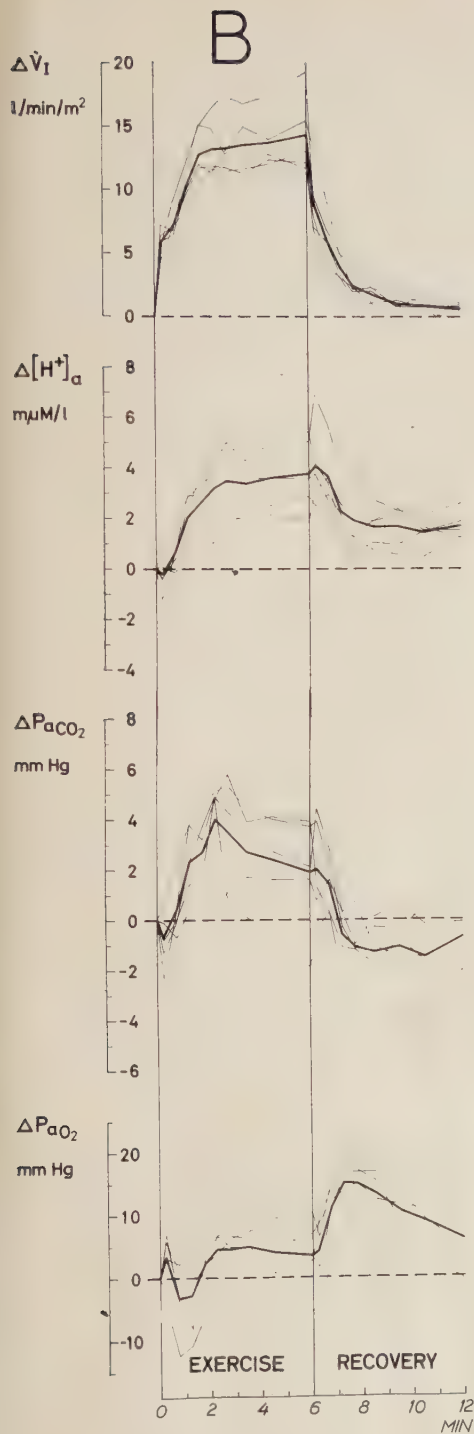


Table IV. Data obtained at rest and during exercise ($n = 7$)

Conditions: *NB* = normal, *HB* = high, *LB* = low BHCO_3Sr .

	$\dot{V}_I$ (1 BTPS/min/m ²)			V_T (1 BTPS/m ²)			S_{aO_2} (%)		
	Rest ¹	Exercise ²	Difference Exercise— Rest	Rest ¹	Exercise ²	Difference Exercise— Rest	Rest ¹	Exercise ²	Difference Exercise— Rest
<i>NB</i>									
M ± S. E.	4.33 ± .15	17.19 ± .84	+ 12.86 ± .89	.318 ± .020	.943 ± .051	.625 ± .042	96.1 ± .1	96.1 ± .2	+ .1 ± .2
S. D.	.39	2.23	2.35	.053	.135	.111	.2	.6	.5
P			< .001			< .001			> .05
<i>HB</i>									
M ± S. E.	3.90 ± .12	17.12 ± 1.03	+ 13.22 ± .97	.315 ± .012	.900 ± .052	.585 ± .053	95.9 ± .2	96.0 ± .2	+ .1 ± .2
S. D.	.32	2.72	2.56	.032	.138	.141	.5	.6	.6
P			< .001			< .001			> .05
<i>LB</i>									
M ± S. E.	5.12 ± .36	20.13 ± .87	+ 15.00 ± 1.07	.349 ± .022	1.033 ± .062	.685 ± .050	96.3 ± .1	96.1 ± .2	— .2 ± .2
S. D.	.95	2.30	2.84	.058	.164	.132	.3	.6	.6
P			< .001			< .001			> .05
<i>HB — NB</i>									
M ± S. E.	— .43 ± .15	— .07 ± .68	+ .36 ± .65	— .003 ± .012	— .043 ± .065	— .040 ± .059	— .1 ± .2	— .1 ± .2	0 ± .2
P	< .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05	> .05
<i>LB — NB</i>									
M ± S. E.	+ .80 ± .31	+ 2.94 ± .62	+ 2.14 ± .90	+ .030 ± .030	+ .090 ± .068	+ .060 ± .046	+ .2 ± .2	0 ± .3	— .3 ± .3
P	< .05	< .01	> .05	> .05	> .05	> .05	> .05	> .05	> .05

¹ Mean value over 3 min.

² Mean of 5th—6th min of exercise.

³ At body temperature.

[H ⁺] _a ^{3, 4} (mμM/l)			P _a O ₂ ^{3, 5} (mm Hg)			P _a CO ₂ ^{3, 6} (mm Hg)		
Rest ¹	Exercise ²	Difference Exercise— Rest	Rest ¹	Exercise ²	Difference Exercise— Rest	Rest ¹	Exercise ²	Difference Exercise— Rest
37.3 ± .7 1.9	41.3 ± 1.0 2.7	+ 4.0 ± .7 1.8 < .01	87.0 ± 1.8 4.7	92.1 ± 2.4 6.4	+ 5.1 ± 1.9 5.3 < .05	37.9 ± 1.1 2.9	41.0 ± .9 2.4	+ 3.1 ± .8 2.1 < .01
34.7 ± .4 1.2	38.5 ± .7 1.7	+ 3.8 ± .5 1.3 < .001	82.6 ± 1.9 5.0	87.7 ± 2.3 6.0	+ 5.1 ± 1.9 5.0 < .05	38.7 ± .9 2.5	41.0 ± 1.2 3.0	+ 2.3 ± .7 1.8 < .05
44.2 ± 1.4 3.8	49.8 ± 1.0 2.5	+ 5.6 ± 1.0 2.6 < .01	95.5 ± 1.5 3.9	99.1 ± 2.5 6.7	+ 3.6 ± 1.5 3.9 < .05	32.0 ± .9 2.4	35.3 ± .9 2.5	+ 3.3 ± 1.2 3.2 < .05
- 2.6 ± .7 < .01	- 2.7 ± .7 < .01	- .1 ± .2 > .05	- 4.4 ± 1.9 > .05	- 4.4 ± 2.5 > .05	- .1 ± 1.7 > .05	+ .8 ± .9 > .05	+ .1 ± 1.0 > .05	- .8 ± .4 > .05
+ 6.9 ± 1.6 < .01	+ 8.6 ± 1.4 < .001	+ 1.7 ± .8 > .05	+ 8.5 ± 2.9 < .05	+ 7.0 ± 3.7 > .05	- 1.5 ± 2.3 > .05	- 5.9 ± .6 < .001	- 5.7 ± 1.0 < .01	+ .2 ± 1.1 > .05

⁴ [H⁺]_a = hydrogen ion concentration of arterial blood in mμM/l.
35 mμM/l = pH 7.456, 40 mμM/l = pH 7.398, 45 mμM/l = pH 7.347, 50 mμM/l = pH 7.301.

⁵ Calculated from O₂-saturation and pH by use of the line charts of SEVERINGHAUS (1958).

⁶ Computed from the HENDERSON-HASSELBALCH equation.

minute, showing a decrease in the second half-minute. P_{aO_2} then increased above its pre-exercise level and remained 4—5 mm Hg higher than in the pre-exercise period. During the first half-minute of recovery P_{aO_2} remained unchanged, and then rose sharply. The rise during recovery was more marked in HB than in NB or LB. After attaining its maximum in the second minute of recovery, P_{aO_2} again rapidly declined.

P_{aCO_2} . The mean time-course of the calculated P_{aCO_2} approximated that of the arterial $[H^+]$ at the very beginning of exercise. In their further courses the two variables diverged, however, due to a decrease of the $BHCO_{3st}$ (*cf.* Calculations p. 17). Thus the P_{aCO_2} reached a peak value in the second and third minutes of exercise, and then declined slowly, as opposed to $[H^+]_a$ which remained relatively constant after the first 2—3 min of exercise. Although in the 5th and 6th min of exercise P_{aCO_2} showed a significant increase of about 3 mm Hg in all three conditions (Table IV), there was a rather wide scatter of the individual increments (Fig. 7). No relation could be found between the magnitude of increase in P_{aCO_2} and the working capacity.

In recovery P_{aCO_2} had a time-course similar to $[H^+]_a$. However, due to the diminished buffering capacity, P_{aCO_2} fell below the pre-exercise level although $[H^+]_a$ remained elevated.

Analysis of Ventilatory Changes at the Start and Cessation of Exercise

For the first 90 seconds of both exercise and recovery a breath-by-breath determination of the respiratory minute volume was made from the continuous recordings of the tidal volumes. From estimates of individual values, the group means of the time-averages for consecutive 6-sec periods were calculated for the first 42 sec. For the remaining time periods the respiratory minute volume was calculated as time-averages over 15-sec periods. The group means have been plotted in Fig. 8.

“On”-Effects. Immediately at the onset of exercise the respiration was increased, and even the very first breath was invariably augmented (*cf.* Fig. 6, p. 29). This very rapid rise of ventilation in the initial stage nearly doubled the ventilation during the first 6 sec of exercise. The initial rise was larger and more distinct in HB and LB (Fig. 8, *B* and *C*). In all three conditions, the ventilatory increase in the first half-minute of exercise corresponded to 40—60 % of the total ventilatory increase in the 5th and 6th min of exercise.

“Off”-Effects. Immediately at the cessation of exercise, there was a sudden decrease in ventilation in all three conditions. The most marked decrease was seen in NB (*A*). Within the first 2—3 breaths, the increase in respiratory minute volume above the resting level was reduced to some two-thirds of the increment in the 5th and 6th min of exercise.

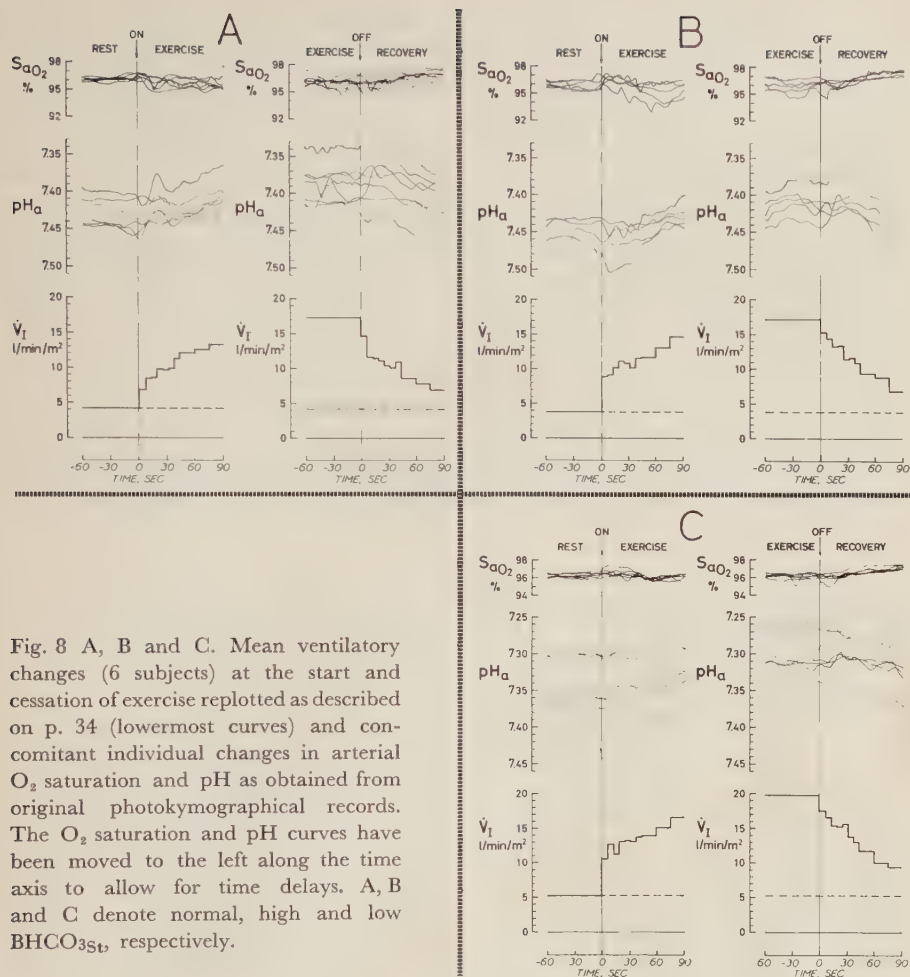


Fig. 8 A, B and C. Mean ventilatory changes (6 subjects) at the start and cessation of exercise replotted as described on p. 34 (lowermost curves) and concomitant individual changes in arterial O_2 saturation and pH as obtained from original photokymographical records. The O_2 saturation and pH curves have been moved to the left along the time axis to allow for time delays. A, B and C denote normal, high and low $BHCO_3$, respectively.

After the initial fall, there was a stage of a secondary, more gradual decrement of ventilation, the beginning of which took place some 20 sec after cessation of exercise.

pH_a and S_{aO_2} . For comparison, the original S_{aO_2} and pH_a -recordings have been replotted on the same coordinates in Fig. 8. The recordings were moved to the left along the time axis to allow for inherent time delays.

During the first 20 seconds of exercise and recovery, the pH_a recordings showed, in general, no consistent changes. After about 30 seconds, all curves changed in the same direction, during exercise in an acid direction, in recovery towards the pre-exercise levels.

Some subjects exhibited a peculiar variation in pH_a at the onset of exercise, with an alkalotic drop immediately after onset of exercise followed by a transient acid wave. However, the mean level of the individual tracings during the first 30 sec was unchanged or showed a slightly acid shift. The alkalotic drop was especially pronounced in subject JF (lowest pH tracings in Fig. 8, *B* and *C*).

The individual scatter in $S_{a_{O_2}}$ was very small. The constancy of the individual tracings during the first half-minute of exercise and recovery was striking in all three conditions. The slight lowering of $S_{a_{O_2}}$ at the end of the first minute of exercise (p. 28) can be especially seen in *B* and *C*.

In summary, the analysis of the respiratory changes at the onset and at the cessation of exercise revealed rapid and large changes of $\dot{V}_I$ in the initial stages of both exercise and recovery. The magnitude of the changes was considerable, amounting to about 50 per cent of the total ventilatory increment during exercise. No consistent changes occurred in the chemical composition of the arterial blood during these initial changes of ventilation.

Increments in $\dot{V}$, Arterial $[\text{H}^+]$ and P_{CO_2} during CO_2 Inhalation and during Exercise and Recovery

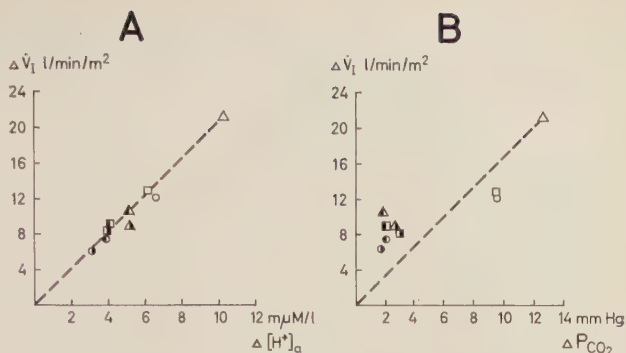
In the preceding two sections it was shown that pulmonary ventilation during moderate, constant-load exercise exhibited an initial rise, followed by a slower secondary increase until a plateau was attained. During recovery, an initial fall occurred, followed by a slower secondary decrease. Furthermore, it was shown that the initial ventilatory changes at the transitions from rest to exercise and from exercise to rest were quite rapid if analyzed on a breath-by-breath basis. By combining the $\dot{V}$ curves of Fig. 7 and 8 one arrives at the typical time-course of $\dot{V}$ showing short-lasting plateaus during the very first stages of exercise and recovery before progressing as shown in Fig. 7. (The result of this operation is schematically represented by the upper curve in Fig. 10, from which the initial fast, and secondary slow changes in $\dot{V}$ during the periods of exercise and recovery are apparent.)

A close study of the individual response pattern of the arterial pH during the period of exercise revealed a striking similarity to that of $\dot{V}$ during what is here referred to as the stage of secondary increase in $\dot{V}$ (*cf.* Fig. 10). Furthermore, the intra-individual relation between the increments in $\dot{V}$ and arterial $[\text{H}^+]$ during this stage seemed to match the individual $\Delta\dot{V}_I/\Delta[\text{H}^+]_a$ slope obtained during CO_2 inhalation at rest (*cf.* upper graphs in Fig. 5). It therefore seemed worthwhile to investigate these relations for the entire group. Fig. 9 A shows the mean increments in $\dot{V}$, as observed (1) in the stage of secondary increase during exercise ($\Delta\dot{V}'$ in Fig. 10) and (2) during CO_2 inha-

Fig. 9. Mean increments in ventilation plotted against those in arterial hydrogen ion concentration (A) and carbon dioxide tension (B) as observed under the following conditions:

1. during CO_2 breathing (open symbols) on shifting from 2.8 % CO_2 to 6.3 % CO_2 in air (*cf.* Table III, absolute values represent time-averages over the 9th and 10th min on each gas mixture).
2. during the stage of secondary increase in exercise (symbols filled on right side).
3. during early recovery (symbols filled on left side).

Circles = normal $\text{BHCO}_{3\text{St}}$; squares = high $\text{BHCO}_{3\text{St}}$; triangles = low $\text{BHCO}_{3\text{St}}$.



lation on changing from one CO_2 fraction to another, both plotted against the concomitant increments in arterial $[\text{H}^+]$.

The relation between increments in $\dot{V}$ and arterial $[\text{H}^+]$ was also studied during recovery. As soon as the fast, initial fall of ventilation had subsided this relation ($\Delta \dot{V}'' / \Delta [\text{H}^+]_a''$ in Fig. 10) assumed a value that was close to the $\Delta \dot{V}' / \Delta [\text{H}^+]_a$ slope during the stage of secondary increase in exercise and for CO_2 inhalation (*cf.* above). That the mean increments in $\dot{V}$ and $[\text{H}^+]_a$ as studied above, were well correlated, is further demonstrated by the fact that the $\Delta \dot{V} / \Delta [\text{H}^+]_a$ relationships were found to yield practically the same slope whether studied in the normal, high or low $\text{BHCO}_{3\text{St}}$ condition (circles, squares and triangles in Fig. 9). It can be seen from Fig. 9 A, that a change in the arterial $[\text{H}^+]$ by one unit (1 mμM/l) corresponded to a ventilatory change of about 2 l/m² body surface.

For comparison, all the relations described above have been plotted with arterial P_{CO_2} substituted for arterial $[\text{H}^+]$ as the abscissa (Fig. 9 B). The information contained in Fig. 9 A and B indicates that, in general, the ventilatory increments during exercise and recovery ($\Delta \dot{V}'$ and $\Delta \dot{V}''$) and CO_2 inhalation, under normal as well as under high and low $\text{BHCO}_{3\text{St}}$ conditions, are better correlated with the concomitant increment in $[\text{H}^+]_a$ than with that of P_{aCO_2} . Fig. 9 also shows that the $\Delta \dot{V} / \Delta P_{\text{aCO}_2}$ slope was steeper during exercise and recovery than following inhalation of CO_2 .

VII. DISCUSSION

Some of the more important conclusions that can be drawn from the results of the present investigation rest upon the comparison of ventilatory changes with rather small changes in arterial $[H^+]$ and P_{CO_2} . The validity of the comparisons will accordingly be dependent on the accuracy achieved in the determination of these changes. Even minute errors in the determination of the changes observed in arterial $[H^+]$ or P_{CO_2} during exercise will appreciably influence the relations described in the last chapter of the results.

It was therefore considered essential that the intraindividual changes in these parameters should be determined with great accuracy. This requirement was fulfilled by the use of continuous recording techniques for arterial pH and S_{O_2} , which have been in use for some years in this laboratory. The drift of the recording system was negligible, and the scatter inherent in spot-sampling techniques was thus avoided.

In the following discussion the results obtained will be dealt with as they occur in the different stages of the ventilatory response to exercise. The characteristic features of this ventilatory response, which have been schematically illustrated in Fig. 10 (upper tracing), consist of a rapid, almost instantaneous rise of ventilation at the onset of exercise, followed by a more gradual increase to an apparently steady state (ASMUSSEN and NIELSEN 1948, DEJOURS 1959). At the cessation of exercise there is a sharp drop in ventilation, followed by a gradual decrement. In the following discussion the nomenclature indicated in the figure will be used in referring to the different stages of the ventilatory response to exercise.

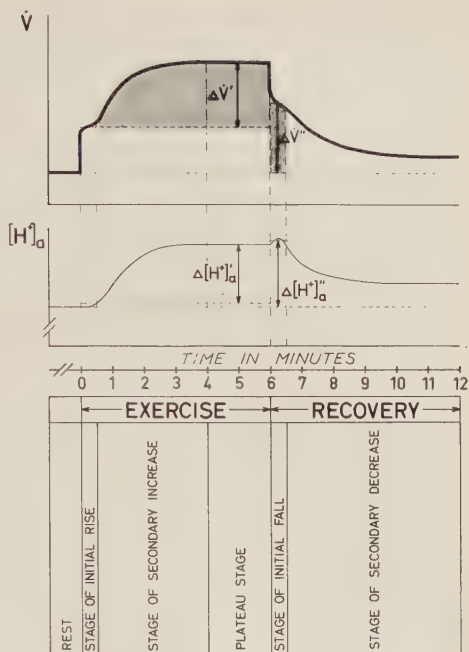
The Transition from Rest to Exercise and from Exercise to Rest

The results of the present investigation clearly demonstrate that the rapid changes in pulmonary ventilation observed at the onset and at the end of the exercise period occurred before any chemical changes in the arterial blood (as recorded or calculated) could have reached central or peripheral chemoreceptors. From the present data, obtained by the use of continuous recording techniques, it seems justified to state that physiologically

Fig. 10. Basic form of the time-course of ventilation ($\dot{V}$) during exercise and recovery as obtained in the present investigation (heavy line). Also shown schematically is the time-course of arterial $[H^+]$ (from arterial pH recordings). The nomenclature used for the various stages in exercise and recovery refer solely to the observed changes in $\dot{V}$.

$\Delta \dot{V}'$ represents the increment of $\dot{V}$ from its mean value during the stage of initial rise to that in the plateau stage, $\Delta \dot{V}''$ represents the difference between the mean value of $\dot{V}$ during the stage of initial fall in recovery and its resting level.

Note that the $\Delta \dot{V}/\Delta [H^+]_a$ ratios in the plateau stage were the same as in the stage of initial fall in recovery.



significant changes in these factors do not occur until after the lapse of about 20—30 sec.

The observation that the ventilation at the onset of exercise increases independently of known arterial stimuli confirms the conclusions of KROGH and LINDHARD (1913b), ASMUSSEN and NIELSEN (1948) and DEJOURS (1959). In this connection it should be noted that the dynamic changes in the arterial P_{CO_2} , as far as the first 20—30 sec are concerned, have in the past always been estimated indirectly from the measured changes in end-tidal or end-expiratory P_{CO_2} . The present investigation has demonstrated, however, that end-tidal P_{CO_2} is only to a limited extent representative of the arterial P_{CO_2} during the various phases of moderate exercise and subsequent recovery. In effect, a considerable rise in the end-tidal P_{CO_2} could be observed at the transition from rest to exercise, although the arterial P_{CO_2} still remained unchanged (*cf.* p. 20). Similarly, the transition from exercise to rest may show a marked fall in the end-tidal P_{CO_2} in the face of an essentially unchanged arterial P_{CO_2} .

From these observations it can then be concluded that the actual changes in the arterial P_{CO_2} are even less than has earlier been surmised on the basis

of end-tidal P_{CO_2} measurements. Hence, the independence of the initial changes in ventilation with respect to the arterial P_{CO_2} at the transition from rest to exercise and from exercise to rest will be fully revealed only if the latter variable is measured directly.

The relatively long-lasting constancy of the arterial gas tensions would imply that the overall ventilation/perfusion ratio of the lung remained constant in early exercise, in spite of the rapid rise in ventilation. This seems to indicate that the rapid ventilatory increase was accompanied by a similar rapid increase of blood flow from the very beginning of exercise. Even a minor phase displacement between the acceleration of circulation and of ventilation would have caused major changes in the composition of the arterial blood.

It thus seems as if the rapid increases in both the circulation and ventilation at the onset of exercise are initiated by neural mechanisms. Because of the close association in time of circulatory and ventilatory changes it is tempting to postulate a common link responsible for the acceleration of both systems, either at the receptor sites, or within the central nervous system. Such a hypothesis does not seem to be incompatible with current knowledge of circulatory adaption to exercise (*cf.* ASMUSSEN and NIELSEN 1955).

It has recently been suggested by ARMSTRONG *et al.* (1961) as well as by RILEY (1963) that pulmonary arterial chemoreflexes sensitive to changes in the composition of the mixed venous blood might contribute to the exercise hyperpnea. It appears unlikely, however, that such chemoreflexes should be able to cause an increased ventilatory response within the first seconds of muscular exercise and thus before mixed venous blood of altered composition reaches the pulmonary artery (*cf.* DEJOURS, MITHOEFER and TEILLAC 1955 b).

The neural stimuli supposed to increase ventilation may be either central or proprioceptive, and evidence has been presented that both types of stimuli may be acting (for review see ASMUSSEN and NIELSEN 1948, and DEJOURS 1959).

Apart from proprioceptive reflexes, other reflex mechanisms may be involved in the initial stage of ventilatory increase. Hypotension may increase the reflexogenic stimulation to breathing from peripheral arterial baro- and chemoreceptors (*cf.* HEYMANS and NEIL 1958). A contribution of hypotension to the exercise hyperpnea has been suggested by KRAMER and GAUER (1941). An arterial pressure drop at the onset of exercise has been demonstrated in man by HOLMGREN (1956), who reported that the fall began some 3–4 sec after the onset of exercise and lasted for about 15 sec. The fall varied between 0–40 mm Hg, and in most cases the reduction exceeded 10 mm Hg. The findings of HOLMGREN have been confirmed in this laboratory (BARR *et al.* 1963). In view of the fact that the initial rise in ventilation reached its peak before this hypotensive drop occurred, it is questionable, however, if such an influence from peripheral receptors can contribute significantly to the initial rise of ventilation in man.

The Role of Chemoreflexes during Exercise and Recovery

During moderate exercise there exists a close adjustment of the pulmonary ventilation to the metabolic needs of the body, so that the ventilatory equivalent ($\dot{V}_E/\dot{V}_{O_2}$) remains constant. As pointed out by GRODINS (1950) an adequate theory of respiratory control must account for this observed relationship between ventilation and oxygen consumption in addition to qualitatively identifying the stimuli and pathways concerned. In view of this precise adjustment of ventilation to the oxygen needs of the exercising body, efforts have logically been made to detect a possible contribution of a hypoxic drive during exercise.

The continuous recording of the oxygen level in the arterial blood revealed a surprising constancy of the arterial oxygen saturation during the course of exercise and recovery. The metabolic alkalosis or acidosis present in conditions HB and LB, respectively, did not change the oxygen saturation significantly, although the arterial oxygen tension values were about 4 mm Hg lower in HB, and about 8 mm Hg higher in LB than in NB. Otherwise the pattern of the changes in oxygen tension was similar in the three conditions (*cf.* Fig. 7). The differences in the oxygen tensions in the three conditions and in the course of exercise were balanced by the changes in the arterial blood reaction so that the oxygen saturation remained almost unchanged. The statement by GRODINS cited above on the constancy of the ventilatory equivalent may apparently be extended to include a notable constancy of the oxygen saturation of the arterial blood as being another factor that must be accounted for in any theory concerning the regulation of ventilation during exercise.

The observation that the arterial oxygen tension was somewhat increased rather than decreased in the plateau stage of exercise agrees with recent results obtained by ASMUSSEN and NIELSEN (1958), LAMBERTSEN *et al.* (1959), McILROY and HOLMGREN (1961) and BARR *et al.* (1963). Earlier observations of a fall in $P_{a_{O_2}}$, especially during heavy exercise (SUSKIND *et al.* 1950, HOLMGREN and LINDERHOLM 1958), might to some extent be explained by the fact that the oxygen tensions were determined at 37° C instead of at the actual body temperature. Another important factor when determining changes in $P_{a_{O_2}}$ is the choice of control level. In the sitting or standing position at rest, $P_{a_{O_2}}$ is a few mm Hg lower than in the supine position due to the effect of posture on the pulmonary gas exchange (*cf.* ULMER and REICHEL 1961, BJURSTEDT *et al.* 1962). Thus, had the control values been obtained with the subjects in the supine position, the increase in oxygen tension during exercise would probably have become about half as great as that observed.

The time-course of the arterial P_{O_2} during moderate exercise has been investigated by SUSKIND *et al.* (1950). These authors found the oxygen tension to be significantly lowered in the second and third minutes of exercise, but

otherwise no significant changes were observed in the 4 min of exercise, and 3 min of recovery studied. In the present investigation a slight decrease was found in the second halfminute of exercise, indicating that $\dot{V}_{O_2}$ increased somewhat faster than $\dot{V}_A$. This transient lowering of the oxygen tension appears to be too small to constitute a significant causative factor of the exercise hyperpnea. GALDSTON and WOLLACK (1947) found that the $P_{a_{O_2}}$ in the first minute of recovery was about 13 mm Hg higher than in the resting supine position. A similar increase was found in the present investigation.

In an earlier investigation from this laboratory (BARR *et al.* 1963) the time-courses of arterial pH and S_{O_2} were investigated during light and moderate exercise without measurement of $\dot{V}_E$. The time-courses of the two variables were found to be almost identical with those obtained in the present investigation. This indicates that the constancy of $S_{a_{O_2}}$ and the increase in $P_{a_{O_2}}$ were not caused by any interference with respiration due to increased external breathing resistance. In a study of the changes in cardiac output during exercise, DONALD, BISHOP and WADE (1954) also determined the time-courses of the changes in arterial S_{O_2} . As judged from their graphs, $S_{a_{O_2}}$ remained approximately unchanged during the course of exercise and recovery.

The observation that the arterial P_{O_2} remains unchanged or even shows a small increase during moderate exercise does not necessarily imply an unchanged or decreased hypoxic chemoreflex drive. The hypoxic drive during exercise has been indirectly studied in man in experiments performed at different degrees of hyperoxia. Numerous such investigations (*e. g.* ASMUSSEN and NIELSEN 1946, 1958, LUNDIN and STRÖM 1947, BANNISTER and CUNNINGHAM 1954, LAMBERTSEN *et al.* 1959, PERRET 1960) have shown that oxygen inhalation diminishes the ventilatory response to exercise, the more so the heavier the work load. Oxygen administration also lowers the lactic acid level during exercise. Conversely, during moderate hypoxia, ventilation is increased in proportion to the increased lactacidemia (*cf.* ASMUSSEN and NIELSEN 1946). However, the effect of high oxygen pressure is not exclusively related to improved oxygenation in the working muscle. Judging from the single-breath O_2 test technique, described by DEJOURS *et al.* (1957a, 1958), the hypoxic chemoreflex drive contributes to some 10—15 % of the exercise hyperpnea during air breathing at sea level, and even more during hypoxia (DEJOURS. 1959, MILIC-EMILI, RAYNAUD and DEJOURS 1960). It appears that the single breath O_2 test provides quantitative information as to the hypoxic chemoreflex part of the ventilatory drive, since the reduction of ventilation following an " O_2 test" occurs within one circulation time. Actually, the ventilatory reduction at rest is maximal about 7 sec after the pulmonary capillary P_{O_2} has attained its maximal value (DEJOURS and MATELL 1962, unpublished observations). The demonstration of a certain hypoxic drive in man during air breathing at sea level agrees with observations in animal experiments of a tonic discharge from the chemoreceptors even at normal oxygen pressures.

(EULER, LILJESTRAND and ZOTTERMAN 1939). EULER and LILJESTRAND (1946) have also demonstrated a diminution in the ventilatory response to electrically induced exercise in animals after denervation of the chemoreceptors.

Interrelationships of Ventilation and Arterial $[H^+]$ and P_{CO_2} during Exercise and Recovery

The total exercise hyperpnea vs. hypercapnic hyperpnea. In condition NB the hyperpnea induced by inhalation of 6.3 % CO_2 in air was of approximately the same magnitude as the hyperpnea in the steady state of exercise. However, the increments in arterial $[H^+]$ and P_{CO_2} during exercise were only about one-half and one-third, respectively, of those induced by CO_2 inhalation. It may thus be concluded that the observed changes in the H^+ - CO_2 complex were much too small to account for the hyperpnea of exercise.

In condition LB, the inhalation of CO_2 caused a more marked hyperpnea. The corresponding changes in P_{aCO_2} , and especially in $[H^+]_a$, were, however, also much larger so that the relation between ventilatory increase and increase in $[H^+]_a$ remained unchanged. The increments in ventilation and $[H^+]_a$ during exercise were somewhat larger than in condition NB, whereas the increase in P_{aCO_2} was approximately the same. These observations indicate that during exercise there seems to be a relation between the ventilatory increase and the increase of $[H^+]_a$.

The stage of secondary increase in $\dot{V}$. When the ventilatory increments during the stage of secondary increase in ventilation were plotted against the concomitant increments in $[H^+]_a$ ($\Delta\dot{V}'/\Delta[H^+]_a'$ in Fig. 10, p. 39), it was found that in all three conditions these points fell close to the $\Delta\dot{V}/\Delta[H^+]_a$ response lines obtained during CO_2 inhalation. The slopes of these CO_2 response lines were almost identical in the three conditions (Fig. 9 A, p. 37). When the same plots were made for the relation between $\Delta\dot{V}'$ and ΔP_{aCO_2} , the points fell to the left of the CO_2 response lines (Fig. 9 B).

The remarkably good correlation between changes in ventilation and changes in arterial $[H^+]$ in all the conditions studied does not seem to have been described previously. From this observation it may be justified to conclude that the response of the respiratory system to changes in arterial $[H^+]$ is the same whether these changes are induced by exercise or by CO_2 inhalation. It also appears that the observed relations between the ventilatory increase in the secondary stage of exercise hyperpnea and the concomitant increments in $[H^+]_a$ give support to those hypotheses which anticipate an interaction of humoral and neural respiratory drives in the generation of the exercise hyperpnea (*cf.* DEJOURS 1959, LAMBERTSEN 1961, and CUNNINGHAM 1963).

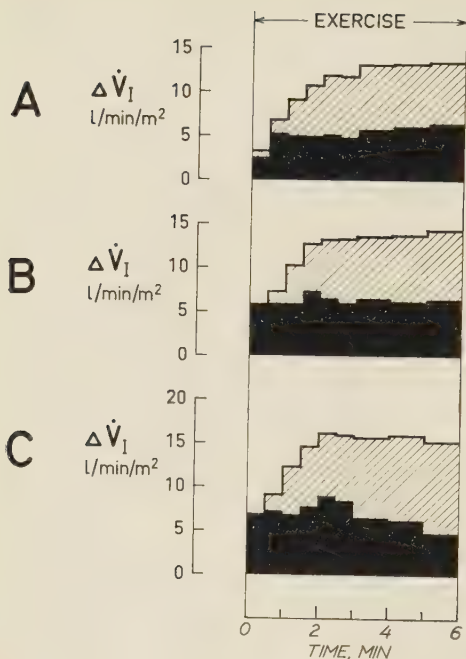


Fig. 11. Schematic representation of calculated humoral and non-humoral components in exercise hyperpnea.

The boundaries of any one graph represent the time-course of the ventilatory increase (above pre-exercise level) during the period of exercise (*cf.* Fig. 7). The hatched area has been obtained from the actual increase in $[H^+]_a$ and the $\Delta\dot{V}/\Delta[H^+]_a$ ratio observed during CO_2 inhalation at rest (chemically accountable ventilation). The black area represents the remaining component of respiratory stimulation.

The graphs are based on data from continuous recordings, which were reduced into group means of individual time-averages determined over the first six 30-sec periods and the ensuing three 60-sec periods during exercise (625 kpm/min for 6 min).

A = Normal $BHCO_{3St}$ ($n = 5$),
 B = High $BHCO_{3St}$ ($n = 5$),
 C = Low $BHCO_{3St}$ ($n = 6$).

The plateau stage of exercise. As shown in Fig. 7 (p. 30) the ventilation and arterial $[H^+]$ remained relatively stable in the 5th and 6th min of exercise. The magnitude of the increase in $[H^+]_a$ agrees with earlier observations (LAMBERTSEN *et al.* 1959, BARR *et al.* 1963). The rather inconsistent pattern of the P_{aCO_2} is also in agreement with findings reported in the literature (*cf.* p. 8).

The share of $[H^+]_a$ in the exercise hyperpnea. The present observation of an essentially unaltered response of the respiratory system to changes in $[H^+]_a$ warrants a tentative analysis of the average share of $[H^+]_a$ in the exercise hyperpnea. This has been done by multiplying the observed increments in $[H^+]_a$ by the value of $\Delta\dot{V}/\Delta[H^+]_a$ obtained during CO_2 breathing. In Fig. 11 these products are indicated by hatched areas, which thus represent the share in the total ventilatory increase induced by increments in $[H^+]_a$. Admittedly, objections may be made against this way of processing the data, *e.g.* because (a) the time necessary for establishing equilibrium between the gases in the blood and the chemosensitive areas is not known, and (b) a possible additive action of P_{aCO_2} as an independent respiratory stimulus has not been accounted for. However, the diagram is not intended to be more than an illustration of the possible relation between ventilation and $[H^+]_a$ obtained in this investigation.

The diagram would then illustrate that the ventilatory increase appearing

after the first half-minute of exercise has a constant relation to the increase in $[H^+]_a$. The black areas, which constitute the remaining part of the total ventilatory increase, would thus correspond to the non-arterial contributions to the respiratory drive, and are believed to include mainly the neural respiratory drives. The fact that these black areas have a rectangular shape gives some support to the view that the neural respiratory drives are acting throughout the exercise period as has been proposed by DEJOURS (1959). This does not imply, however, that the neurogenic drive remained constant. Such factors as *e. g.* body temperature and adrenaline levels may also contribute to the exercise hyperpnea. Since the temperature rise observed in the present investigation amounted only to some tenths of a degree, it is believed that the rise in temperature contributed but little to the exercise hyperpnea.

The hyperpnea of recovery. After the initial rapid fall in ventilation, the ratio $\Delta\dot{V}''/\Delta[H^+]_a''$ in early recovery (*cf.* Fig. 10, p. 39) had the same value as $\Delta\dot{V}'/\Delta[H^+]_a'$ during exercise. Later in recovery ventilation decreased faster than the hydrogen ion concentration. This may to some part be explained by a probable decrease in hypoxic stimulation during recovery, but it also seems that other, unknown factors contributed to this ventilatory decrement.

Concluding remarks. The present investigation has shown that, irrespective of the buffering capacity of the blood, there was the same relation between changes in $[H^+]_a$ and ventilation both during CO_2 inhalation and during the secondary stages of ventilatory changes in response to exercise. No such constant relation was found between changes in P_{aCO_2} and ventilation. This does not necessarily imply, however, that H^+ is the "unique respiratory stimulus". A differentiation between the physiological action of $[H^+]$ and P_{CO_2} is rendered difficult by the fact that changes in P_{CO_2} are accompanied by concurrent alterations of $[H^+]$, if $BHCO_{3st}$ remains constant.

In this connection it should be emphasized that the observed correlation between ventilation and $[H^+]_a$ seems to be valid only in acute experiments. This conclusion is based on the observation that the longlasting acidemia induced by ammonium chloride ingestion was associated with only a slight increase of the resting ventilation, which is in agreement with earlier observations of *e. g.* NIELSEN (1936).

Available data seem to indicate that a number of respiratory stimuli contribute to the hyperpnea of exercise. The coarse adjustment of ventilation appears to be of neural origin and related to the rhythm, strength and degree of engagement of the musculo-skeletal system. Humoral stimuli seem to be responsible for the fine and precise adjustment of ventilation to the metabolism, apparently in a similar way as in the resting condition.

In this investigation, the two main groups of stimuli seemed to be responsible for about equal parts of the hyperpnea during exercise. If the same relation exists for other loads and types of work remains to be investigated.

VIII. SUMMARY

In an attempt to assess quantitatively the role of possible chemical stimuli in the hyperpnea of exercise, the time-courses of ventilation, arterial O_2 saturation and pH (and concomitant calculated changes in arterial P_{O_2} and P_{CO_2}) were studied in 7 healthy male subjects during moderate, constant-load exercise (625 kpm/min for 6 min) and ensuing recovery (6 min), both under normal and under high and low $BHCO_{3\text{ST}}$, the two last-mentioned conditions being induced by ingestion of ammonium chloride and sodium bicarbonate, respectively.

1. *Ventilatory and blood chemical responses.* At the onset of exercise ventilation increased in a stepwise fashion, and after some 20—30 sec showed a secondary increase to attain a plateau after about 3 min of exercise. At the cessation of exercise ventilation first fell steeply and after 20—30 sec showed a secondary, more gradual decrease towards its pre-exercise level.

The arterial O_2 saturation remained remarkably constant throughout the period of exercise, whereas the O_2 tension, after a transient drop, increased by about 5 mm Hg. In recovery, the O_2 saturation increased by about 1 %, and the O_2 tension by about 15 mm Hg during the first 2 min, and then declined.

Arterial $[H^+]$ and P_{CO_2} remained essentially constant for the first 20—30 sec following the onset and cessation of exercise. During the remainder of the period of exercise arterial $[H^+]$ increased gradually to reach a plateau after 3—4 min. The arterial P_{CO_2} (mean for the group) was elevated at the end of exercise; however, some individuals showed a decrease below resting levels.

During the remainder of the period of recovery, arterial $[H^+]$ showed a gradual decrease towards pre-exercise levels. The arterial P_{CO_2} (mean for the group) gradually fell below the pre-exercise level.

The observation that the initial rise and fall of ventilation in exercise and recovery, respectively, occurred without significant changes in arterial O_2 , H^+ or CO_2 levels, suggests that these fast components of exercise hyperpnea are controlled by other factors.

2. *Assessment of H^+ and CO_2 stimuli in exercise hyperpnea.* On determining individual and mean responses to CO_2 inhalation at rest and analysing these responses in terms of slopes ($\Delta\dot{V}/\Delta[H^+]_a$ and $\Delta\dot{V}/\Delta P_{aCO_2}$), the mean $\Delta\dot{V}/\Delta[H^+]_a$ slopes during the secondary increase in exercise hyperpnea and during the first half-minute of recovery (subtracting the initial decrement in ventilation) were found to coincide with the $\Delta\dot{V}/\Delta[H^+]_a$ slope obtained during CO_2 inhalation ($2\text{ l/m}^2\text{ BSA/m}\mu\text{M/l}$).

The $\Delta\dot{V}/\Delta[H^+]_a$ and $\Delta\dot{V}/\Delta P_{a_{CO_2}}$ slopes, as defined above, were investigated under normal, as well as under high and low $BHCO_{3st}$. In general, the $\Delta\dot{V}/\Delta[H^+]_a$ slopes were about the same in all three conditions whereas the $\Delta\dot{V}/\Delta P_{a_{CO_2}}$ slopes were steeper in exercise and recovery than under CO_2 inhalation, especially in the low $BHCO_{3st}$ condition.

Evidence is presented that the slow ventilatory increase in the secondary stage of exercise hyperpnea is related to the increase in $[H^+]_a$.

3. *Other results.* It was observed that during exercise the arterial to end-tidal P_{CO_2} difference became reversed (mean — 3.1 mm Hg). Also during inhalation of 6.3 % CO_2 a small negative difference (mean — 0.9 mm Hg) was found. The mechanisms underlying these reversals of the P_{CO_2} difference have been discussed.

Ingestion of ammonium chloride (2.5 meq/kg body weight for 3 days) lowered the $BHCO_{3st}$ by 9.5 mM/l, and ingestion of equivalent amounts of sodium bicarbonate increased the $BHCO_{3st}$ by 3.4 mM/l, the normal value being 26.0 mM/l. The lowering of the $BHCO_{3st}$ caused by exercise was not markedly different in the three conditions. No significant differences were observed between the three conditions as to oxygen uptake, RQ, and heart rate at rest or during exercise.

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